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RISK ASSESSMENT ISSUES, INCLUDING LUNG CANCER AND RESPIRATORY EFFECTS

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REVISED COMMENTS ON THE 1986 SURGEON GENERAL'S REPORT, THE EPA DRAFT RISK ASSESSMENTS, THE NIOSH CURRENT INTELLIGENCE BULLETIN, AND OTHER RISK ASSESSMENTS ON ETS

The conclusions of reports by three governmental agencies have been extensively relied upon by various organizations and individuals in discussions of health effects purportedly associated with environmental or "passive" tobacco smoke (ETS) exposure in the workplace. These reports are:

[1] The Health Consequences of Involuntary Smoking,[1] a 1986 report of the Surgeon General (hereinafter 1986 Surgeon General's Report);

[2A] Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children (EPA/600/6-90/006A),[2A] a review draft released by the Environmental Protection Agency (EPA) in 1990 (1990 Draft Risk Assessment);

[2B] Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (EPA/600/6-90/006B),[2B] a review draft released by the Environmental Protection Agency (EPA) in 1992 (1992 Draft Risk Assessment); and

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[2C] Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (EPA/600/6-90/006F),[2C] a risk assessment released by the Environmental Protection Agency (EPA) on January 7, 1993 (Final Risk Assessment); and

[3] Environmental Tobacco Smoke in the Workplace: Lung Cancer and Other Health Effects,[3] a Current Intelligence Bulletin issued by the National Institute for Occupational Safety and Health in 1991 (NIOSH CIB).

These reports have taken on importance in the context of the OSHA RFI to the extent that OSHA RFI commenters may try to rely upon these documents (and other published risk assessments, also discussed herein) in urging OSHA to regulate smoking in the workplace. As underscored in the following comments, these review papers do not provide a basis for regulation of smoking in the workplace by OSHA.

1986 Surgeon General's Report

The EPA draft risk assessment and the NIOSH CIB rely extensively on the conclusions of the 1986 Surgeon General's Report on "Involuntary Smoking," the U.S. Public Health Service's eighteenth report, and the fifth report issued during the tenure of C. Everett Koop. The 1986 Surgeon General's Report reached

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two major conclusions which some may urge are relevant to the workplace smoking issue:

> Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers. (p. vii)
>
> The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke. (p. vii)

The Surgeon General's review has been challenged by a number of critics. One reviewer, Ann Fettner, suggested that the Surgeon General's conclusions were based on "flimsy" evidence presented in an effort to "divert our attention" from important health concerns such as the "poisoning of the environment."[4] A U.S. Congressman, Walter B. Jones, in a letter published in the Congressional Record, wrote that "the conclusions in the Surgeon General's Report are not supported by the research in his own report."[5] The Surgeon General's conclusions regarding lung cancer, cardiovascular disease, adult respiratory disease, and separation of smokers and nonsmokers are relevant to OSHA's current considerations of the workplace environment and will be discussed below in some detail.

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Lung Cancer

The Surgeon General's conclusion that a causal relationship exists between ETS exposure and lung cancer in nonsmokers was based on 13 epidemiologic studies of women whose husbands smoked. Of those studies, eleven reported risk estimates that were not statistically significant.[6] Moreover, scientific deficiencies in the epidemiologic studies on ETS and nonsmoker lung cancer have been identified by numerous individuals. A German specialist in biometrics and epidemiology, Karl Uberla, in his assessment of these studies, suggested that the data fail to meet the criteria which some regard as necessary to establish a causal relationship:[7]

> The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biologic plausibility can be judged controversially.

An eminent American statistician, Nathan Mantel, has also observed:[8]

> [I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith according to one's choice.

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There are currently 30 spousal smoking studies, 24 of which report risk estimates that are not statistically significant.[9-38] Only six studies report statistically significant increased lung cancer risks for women whose husbands smoke. Thus, these studies taken as a group, or considered individually, do not convincingly support rejection of the null hypothesis of no association between ETS exposure and lung cancer in nonsmokers, and therefore are inadequate as a basis for regulatory action.

Moreover, the vast majority of the spousal smoking studies report risk estimates that are less than 2.0. These values are at the limit of detection for epidemiology. Risk estimates below 2.0 or 3.0 have been described as "weak," and thus, any conclusions drawn from such studies are unreliable.[39] This is particularly true when the studies themselves fail to account for numerous sources of bias and confounding factors. The confounding factors are variables associated with both the classification of "marriage to a smoker" and with risk factors associated with lung cancer, the existence of which can give rise to a spurious ETS-lung cancer association. Examples of confounding factors that are not controlled for in the studies include diet, alcohol consumption, cooking and heating methods, occupation, physical activity, urbanization and socioeconomic class.[40]

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In addition, application of spousal smoking studies to the workplace presents significant questions. Even the Surgeon General conceded that "[m]ore accurate estimates for the assessment of exposure in the home, workplace, and other environments are needed" (p. 101).

In fact, the epidemiologic studies on lung cancer and respiratory disease cited in the Surgeon General's Report did not include any actual measurements of study subjects' exposure to ETS in either the home or the workplace. Instead, the studies relied on questionnaire information to estimate exposure to ETS. The Surgeon General's Report itself acknowledges that the "possibility of reporting bias must be considered for the studies that have used questionnaires to measure illness experience" (p. 38). A number of researchers have reported that exposure misclassification can lead to improper indices of exposure and incorrect estimations of risk.[10,41-46] The Surgeon General's Report also concedes that "validated questionnaires are needed for the assessment of recent and remote exposure to environmental tobacco smoke in the home, workplace, and other environments" (p. 107). The National Research Council and other authors have recently criticized questionnaires used in ETS studies for not being standardized or validated, pointing out that misclassification of exposure may occur if the questionnaire is not appropriately designed.[47-49]

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Separation of Smokers and Nonsmokers

The Surgeon General's Report also concluded that "simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, exposure of nonsmokers to environmental tobacco smoke" (p. vii). The Report concludes that smoking bans will not only reduce ETS exposures, but will also "alter smoking behavior and public attitudes about tobacco use" (p. 322). The Report further suggests that "over time, this may contribute to a reduction of smoking in the United States" (p. 322). Thus, the underlying motivation for the use of the ETS/health argument is to attain a "smoke-free society by the year 2000."

The Surgeon General's claim that separation of smokers and nonsmokers does not minimize nonsmoker exposure to ETS is without scientific support. Studies aboard commercial aircraft and in offices indicate, contrary to the Surgeon General's Report, that the simple separation of smokers and nonsmokers effectively minimizes nonsmoker exposure to ETS.[50-57] One recent study, for example, reported that the use of designated smoking areas reduced exposure to ETS by 95 percent.[50] Another study of a smoking-restricted office building reported that ambient nicotine in nonsmoking areas was virtually undetectable, suggesting that ETS had a negligible impact on the nonsmoking areas in the building.[51]

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In addition, Canadian researchers Sterling, et al., in a series of studies, collected data on levels of ETS constituents in offices with different smoking policies. They reported no significant differences in average ETS constituent levels between nonsmoking offices that received recirculated air from designated smoking areas and nonsmoking offices that did not receive recirculated air.[52-53,57] They concluded:

> The results indicate that the provision of a designated, but not separately ventilated smoking area can effectively eliminate or drastically reduce most components of environmental tobacco smoke from nonsmoking offices.

Adult Respiratory Disease

The Surgeon General's Report also addressed purported changes in pulmonary function in adults reportedly exposed to ETS. The Surgeon General concluded that

> healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone. (p. 13)

Two major research groups have examined the possible association between exposure to ETS in the workplace and pulmonary function in adult nonsmokers. White and Froeb reported, based on

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their measurements of the small airways function of smokers and nonsmokers in the workplace, that nonsmokers exposed to tobacco smoke at work for 20 or more years had reduced function of the small airways compared to nonsmokers who did not have such exposures.[58]

The White and Froeb study has been criticized for numerous reasons, including its assessment of ETS exposure and its method of subject selection.[59-62] Furthermore, White and Froeb themselves noted that the average values of the pulmonary tests of nonsmokers exposed to tobacco smoke "were not notably different" from the values suggested as normal by a specialist in this area.[63] Dr. Michael Lebowitz of the University of Arizona wrote the following regarding the White and Froeb study:[64]

> Even with a biased population, poor study design, and incorrect statistical evaluation, there were no clear-cut, consistent, medically meaningful differences between passive smokers and groups of nonsmokers; a corrected statistical analysis strengthened this conclusion.

Moreover, the Surgeon General wrote:

> The [White and Froeb] study population was self-selected, and the exposure classification was crude and did not account for people who changed jobs. (p. 60)

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In addition to these concerns, the results of White/Froeb appear to be inconsistent with those of a second research group, Kentner, et al., who reported no effect of ETS on pulmonary function measurements among 1,351 German office workers.[65] In a 1988 update of the study, Kentner and colleagues noted that[66]

> there is no evidence that average everyday passive smoke exposure in the office or at home leads to an essential reduction of lung function in healthy adults.

The key investigator for the study reported these same findings in 1989 and 1990 publications.[67,68]

The Surgeon General's Report also addressed the issue of acute effects on the pulmonary function of adult nonsmokers exposed to ETS, the Surgeon General concluded that "the magnitude of these changes is quite small, even at moderate to high exposure levels, and it is unlikely that this change in airflow, per se, results in symptoms" (p. 63). The studies available on asthmatic adults are clinical studies that have potential applicability to the home and the workplace setting. However, the studies that have reported an association between exposure to ETS and reactions in asthmatics have several problems. Regarding the studies on asthma in adults, the Surgeon General wrote:

> Acute exposure in a chamber may not adequately represent exposure in the general environment.

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> Biases in observation and the [sic] in selection of subjects and the subjects' own expectations may account for the widely divergent results. Studies of large numbers of individuals with measurement of the relevant physiologic and exposure parameters will be necessary to adequately address the effects of environmental tobacco smoke exposure on asthmatics. (p. 65)

Cardiovascular Disease

The Surgeon General's 1986 conclusion on cardiovascular disease and ETS was that further studies "are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease" (p. 14). In 1988, Fielding, et al., reviewers from the University of California-Los Angeles, who are critical of smoking, conceded that "no firm conclusion that a causal relation exists is yet warranted" for reported ETS exposures and cardiovascular disease.[69] A similar view was expressed in a 1988 review from a Harvard physician, who said that there were "no clear data" that ETS increases heart disease risk.[70]

Several additional evaluations of the literature on ETS and heart disease appeared in 1990. Two of these were reported at international conferences in Lisbon, Portugal[71] and in Budapest, Hungary.[72] Both argued strongly that the data on ETS and heart disease were methodologically weak and insufficient to draw conclusions. In another major review, this one from the United States, two physicians, Drs. Mahajan and Huber, concluded that

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"the data that are available are so sparse that any attempt to reach a definitive assessment would be fraught with uncertainty."[73] Perhaps the most recent review of the literature on ETS and heart disease was published in 1991 by A.K. Armitage, the former director of toxicology of a major European research laboratory.[74] He described the scientific data relating to a possible heart disease risk in nonsmokers exposed to ETS as "not very convincing."

In summary, the Surgeon General's claims that exposure to ETS increases the risk of lung cancer in nonsmokers and that simple separation of smokers and nonsmokers is ineffective in minimizing exposure are not convincingly supported by the scientific data and should not be used as a basis for workplace smoking policy decisions.

EPA Draft Risk Assessment

In June, 1990, the United States Environmental Protection Agency (EPA) released for review a Draft Risk Assessment on ETS.[2A] The 1990 Draft Risk Assessment concluded that exposure to ETS is causally related to lung cancer in adult nonsmokers and is associated with respiratory disease and respiratory symptoms in children. The 1990 Draft Risk Assessment also concluded that ETS should be classified as a Group A ("known human") carcinogen. It estimated that ETS exposures are responsible for 3,800 nonsmoker

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lung cancer deaths per year in the U.S. (the estimate was later revised to 3,700). The Scientific Advisory Board (SAB) for the EPA reviewed the 1990 Risk Assessment in a meeting in December, 1990. Their report, presented to the SAB Executive Committee in April, 1991, suggested that while further revisions were needed, the conclusions of the Draft were sound.

In May, 1992, the EPA released its revised Draft Risk Assessment on ETS.[2B] The revised Draft Risk Assessment again concluded that exposure to ETS is causally related to lung cancer in adult nonsmokers. The revised Draft also concluded that ETS exposures are causally related to respiratory diseases and symptoms in children and added numerical estimates of risk for various respiratory conditions. The revised Draft Risk Assessment again concluded that ETS should be classified as a Group A ("known human") carcinogen. However, the EPA lowered its estimated number of U.S. lung cancer deaths purportedly attributable to ETS exposure to 3,000 per year. This revised Draft Risk Assessment was reviewed by the EPA's SAB Committee in July, 1992. More charges for revisions were made to the EPA staff, but the committee once again endorsed the Draft's conclusion. An Executive Committee meeting of the EPA-SAB took place in October, 1992. The Executive Committee endorsed the SAB committee's report, and the Draft was sent back to EPA staff for minor revisions.

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On Thursday, January 7, 1992, at a press conference, EPA Administrator William Reilly and Secretary Sullivan of the Department of Health and Human Services released the final EPA document, entitled, "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders."[2C] The document classifies ETS a Group A ("known human") carcinogen. This is the first EPA risk assessment based solely upon epidemiologic data in which a substance has been designated a Group A carcinogen.

All three versions of the EPA Risk Assessment employ a Population-Attributable Risk model for estimating excess lung cancer mortality among nonsmokers reportedly exposed to ETS.[2A,2B,2C] This model is based essentially upon three estimates:

1. a point estimate or relative risk derived from a meta-analysis of epidemiologic studies on nonsmoking wives married to smokers;

2. the proportion of nonsmokers in the general (U.S.) population reportedly exposed to ETS; and

3. the total number of nonsmokers in the general population.

To calculate the Population-Attributable Risk (PAR), the authors of the 1990 Draft Risk Assessment estimated that 60% of all nonsmokers are exposed to ETS. A cumulative relative risk of 1.28 was calculated in the 1990 Draft via meta-analysis from epidemiologic studies on spousal smoking as the estimated excess

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risk due to ETS exposure. The PAR for these two assumptions (with other minor adjustments) is 0.27. The total number of deaths for nonsmoking males and females was then estimated, based on the American Cancer Society's projections for 1988 (9,500 total deaths). By multiplying the PAR (0.27) by 9,500, the authors generated an estimate of 2,560 total deaths per year attributable to ETS exposure among neversmokers. A PAR was also computed for male and female former smokers, generating a total estimate of 3,800 excess deaths annually purportedly attributable to ETS exposure among nonsmokers in the United States. Using the same procedure in the 1992 Draft, the authors performed a meta-analysis of the then available eleven U.S. spousal smoking studies and reported a relative risk of 1.19. The calculated cumulative risk generates an estimate of 3,000 excess deaths per year among nonsmokers. The EPA did not modify its 1992 Draft estimate in the final risk assessment document.

The PAR method employs estimates of relative risk, population fractions of exposure to ETS and lung cancer death rates for the general nonsmoking population in order to generate an estimate of excess mortality reportedly attributable to ETS exposure. It is important to note at the outset that the PAR model itself does not determine that there is an increased risk of lung cancer among nonsmokers from ETS exposure. Rather, the model assumes a causal relationship between ETS exposure and an increased risk of lung cancer among nonsmokers, based upon increased risks

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reported in epidemiologic studies on spousal smoking. These reported relative risks are, in turn, assumed to represent true relative risks for the entire population due to ETS exposure.

These critical assumptions have been challenged.[75] To achieve a cumulative excess risk estimate of 1.28 for nonsmokers reportedly exposed to ETS, the authors of the 1990 Draft Risk Assessment performed a meta-analysis of 23 epidemiologic studies on spousal smoking. Eighteen of the studies on spousal smoking included in the EPA's meta-analysis in 1990 fail to achieve statistical significance and are, therefore, consistent with the null hypothesis of no association between spousal smoking and an increased risk of lung cancer among nonsmokers.

The meta-analysis in the 1992 Draft was performed on eleven available U.S. spousal smoking studies, none of which originally reported an overall statistically significant risk estimate. Nevertheless, the EPA reanalyzed the data, using 90% confidence intervals, and reported statistical significance for one risk estimate. The EPA's meta-analysis generated a summary risk estimate of 1.19 for nonsmoker lung cancer. Using a 90% confidence interval, the EPA reported that this risk estimate was statistically significant and that it indicated a causal relationship between spousal smoking and nonsmoker lung cancer. The EPA justified their choice of the 90% confidence interval by referring to a "one-tailed"

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statistical test. The one-tailed test presumes causation: it is designed to show the extent of a purported "effect."

The choice of confidence interval was criticized in a presentation at the October SAB Executive Committee meeting, by James J. Tozzi. In a follow-up letter to the EPA, Tozzi included a meta-analysis of 13 U.S. studies which is not statistically significant using a 95% confidence interval.[76] Tozzi reported a relative risk of 1.07 (95% C.I.: 0.95 to 1.21). Nonetheless, the EPA did not choose to modify their statistical calculations in the final risk assessment document. The main difference between the Tozzi meta-analysis and the EPA meta-analysis was that the Tozzi analysis included two recent lung cancer studies that did not report an association between spousal smoking and lung cancer in nonsmoking wives. The EPA omitted from its risk assessment the NCI-funded Brownson, et al., study, one of the largest and most recent studies on ETS and lung cancer, which found no increase in risk from exposure to ETS.[77] They also omitted the Stockwell et al., 1992, study.[78] If the EPA had included the Brownson and Stockwell studies in its meta-analysis, its risk assessment would not have resulted in a statistically significant increased risk of nonsmoker lung cancer reportedly associated with exposure to ETS.

Eleven of the epidemiological studies EPA considered in the 1992 Draft Risk Assessment included estimates of workplace

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exposures. Ten of those eleven studies reported no statistically significant increased risk for nonsmoking females. If the data on workplace exposures are pooled in a meta-analysis, the risk estimate is below 1.00 (unity), which indicates no positive association between reported workplace exposures to ETS and lung cancer in nonsmokers. However, the Draft Risk Assessment did not consider those important data. The EPA also excluded from consideration over 25 studies on childhood respiratory disease and parental smoking which did not report an effect from parental smoking. It also excluded from its analysis published criticisms of epidemiologic studies on spousal smoking and lung cancer.

The epidemiologic studies on spousal smoking contain no actual exposure data on ETS. The 1990 and 1992 EPA Drafts instead assumed the validity of questionnaire responses about possible exposure to ETS based upon spousal smoking and then generalized these responses to the general population's exposure to ETS. The authors of the 1990 and 1992 Draft Risk Assessments also failed to consider and adequately adjust for confounding factors, e.g., diet, lifestyle, genetics, etc., in any of the individual studies on spousal smoking. This is a significant oversight, especially when dealing with "weak" relative risks which approximate 1.3 in the 1990 Draft Risk Assessment and only 1.19 in the 1992 Draft. When dealing with relative risks this small, spurious associations may be reported between two factors. For example, because the EPA

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did not adequately address the potential role of diet, there is a chance that the association the EPA reported between ETS exposure and nonsmoker lung cancer may actually be a result of a common association the two factors may have with poor diet.

The Draft's assumption of causality is based upon tenuous data from epidemiologic studies on spousal smoking. The assumption is the critical element to the PAR model and the original estimate of 3,800 (and revised estimate of 3,000) excess nonsmoker deaths per year reportedly due to ETS exposure. The 1990 and 1992 Draft Risk Assessments fail to argue convincingly for the assumption. Without the causal assumption, the PAR approach is little more than an exercise in mathematical modeling.

The conclusions of the 1990 Draft Risk Assessment were strongly criticized, particularly in many of the more than 100 comments submitted during the public comment period on the draft.[75] Specifically, many of the public comments found EPA's classification of ETS as a Group A carcinogen to be scientifically unwarranted.

One point of criticism was that the EPA's proposed classification of tobacco smoke as a "human carcinogen" was based in part upon the imputed identification and presence in ETS of suspected carcinogens reported in mainstream smoke and/or fresh sidestream smoke. However, the EPA apparently did not review the

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available published data on either the characterization of, or exposure to, ETS. ETS is neither chemically nor physically equivalent to either mainstream or sidestream smoke, and it is therefore not scientifically acceptable to treat ETS, mainstream smoke and sidestream smoke as qualitatively and quantitatively similar mixtures.[79-84]

As discussed above, meta-analysis, a statistical procedure which combines the reported risk estimates from a number of studies to generate an overall estimate of risk, was used in the EPA's Population-Attributable Risk model. The problems and limitations of the use of meta-analysis for epidemiologic studies have been addressed in the scientific literature.[85,86] For instance, meta-analysis does not account for intrinsic bias and confounding in the individual studies, and it cannot remedy study design flaws. As two German scientists, Heinz Letzel and Karl Uberla, noted: "Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers."[86] The spousal smoking studies used in the 1990 meta-analysis were conducted in the United States, Europe and Asia. These populations differ genetically and in lifestyle factors, and the studies themselves differ in design.[85] The 1992 Draft included separate meta-analyses for the different countries and regions.

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Another major criticism of the 1990 Draft Risk Assessment was that in addition to its inadequate treatment of the data on the physical and chemical properties of ETS, it also virtually ignored the available exposure data, toxicological data and data from animal studies on ETS. The 1992 Draft similarly failed to consider these data. For instance, not one of the spousal smoking studies included actual measurements of ETS exposure; exposure was only estimated by responses to questionnaires. However, a large body of literature exists on actual measurements of ETS in indoor environments, which was not considered in the 1990 Draft Risk Assessment and only cursorily considered in the 1992 Draft.[52,79,87-90] While these data are independent of the epidemiologic literature, they suggest that nonsmoker exposure to ETS in typical public places and workplaces is minimal.[52,87-90] For example, some studies report typical measurements of nicotine ranging from an exposure equivalent of 1/100 to less than 1/1,000 of one filter cigarette per hour.[56,91-97]

While written comments were not accepted on the 1992 Risk Assessment, oral comments were allowed at both the July SAB committee and the October Executive Committee meetings. However, commenters were asked not to reiterate previous points of discussion. One major issue raised by Dr. William J. Butler in July was the EPA's treatment of confounders.[98] The EPA took the position that confounders could not account for the reported

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association between spousal smoking and nonsmoker lung cancer, since the EPA was unable to find a single confounding factor that could consistently account for the results reported in all of the studies used in the Draft Risk Assessment. Butler criticized the EPA's position and stated that there were many potential confounders that should be considered important, and that it was not necessary (or even reasonable to expect) to identify a single confounder that would apply to all of the individual studies.

Finally, if the EPA had followed its own 1986 guidelines for carcinogen risk assessment, it would have included: (1) a hazard evaluation which would have examined data regarding the physical and chemical characterization of ETS, as well as the results from published animal inhalation studies and in vitro studies; (2) an exposure evaluation which would have included the data from well over 100 studies in the published literature which monitored ETS constituents in the air of public places and workplaces; (3) a dose-response evaluation which would have included an examination of the actual data reported in the epidemiologic studies on spousal smoking; and (4) a risk characterization which would have included the range of uncertainty in numbers of lung cancer deaths reportedly attributable to ETS exposures. The guidelines also require that chance must be ruled out statistically in all epidemiologic studies under consideration

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and that all possible biases and possible confounding factors are to be considered.

Thus, the conclusions of the EPA's 1990 and 1992 Draft Risk Assessments are based on an incomplete and selective review of the existing data on ETS. Several of the public comments on the 1990 Draft suggested that this amounted to EPA's apparent failure to follow its own guidelines for carcinogen risk assessment.[75] In fact, the EPA would not have classified ETS as a Group A carcinogen had the EPA used the methodologies and guidelines it employed in all its previous risk assessments.

NIOSH Current Intelligence Bulletin

In June 1991, NIOSH released Current Intelligence Bulletin 54 on environmental tobacco smoke.[3] The NIOSH CIB stated that:

> NIOSH has determined that the collective weight of evidence (i.e., that from the Surgeon General's reports, the similarities in composition of MS and ETS, and the recent epidemiologic studies) is sufficient to conclude that ETS poses an increased risk of lung cancer and possibly heart disease to occupationally exposed workers. (p. 12)

In the excerpt above, the CIB refers to three areas that contribute to its "collective weight of evidence." The Surgeon

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General's report is the first area; however, the conclusions of the Surgeon General's report have been extensively criticized, as discussed above. As for the second type of "evidence" (the claimed "similarities in composition of MS and ETS"), the treatment of the available data in the NIOSH CIB is neither detailed nor complete.

Although the NIOSH CIB and the EPA Draft Risk Assessment stress the reported association between active smoking and disease in reaching their conclusions about ETS, neither report provides detailed discussions of the chemical and physical natures and differences between ETS and mainstream smoke (MS). ETS is different in both quality and quantity from both mainstream and sidestream smoke. (See Responses to Questions 2a(iii) and 35.)

One major area overlooked by both the NIOSH CIB and the EPA Draft Risk Assessment is those scientific studies that actually measured levels of ETS constituents in indoor air. There is a substantial body of literature in this area which is directly relevant to considerations about non-industrial workplace exposure. If the actual data on ETS exposures in the workplace are examined, one finds that typical workplace exposures to ETS are minimal and often below limits of detection for even the most sensitive tobacco smoke constituent monitors. (See Response to Question 2a(iii).)

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The final aspect of NIOSH's "weight of the evidence" is "recent epidemiologic studies" on ETS and lung cancer. However, its review of the spousal smoking studies is incomplete. The CIB states that eight additional spousal smoking studies have been published since 1986, when, actually, 14 have been published, most of which report associations which do not achieve statistical significance. Furthermore, the CIB acknowledges serious shortcomings in the available epidemiologic studies purporting to relate ETS exposure and lung cancer:

> NIOSH recognizes that these recent epidemiologic studies have several shortcomings: lack of objective measures for characterizing and quantifying exposures, failure to adjust for all confounding variables, potential misclassification of ex-smokers as nonsmokers, unavailability of comparison groups that have not been exposed to ETS, and low statistical power.

Nevertheless, the CIB uses spousal smoking studies to reach its conclusion about occupational exposure to ETS without justifying the relevance of spousal smoking studies to workplace exposure. Of the spousal smoking studies, none actually measured levels of ETS to which the subjects ostensibly were exposed. The NIOSH CIB also fails to address the 12 spousal smoking studies that included specific questions about workplace exposure.[9-20] Of those studies, ten reported no statistically significant increased risk of lung cancer for nonsmokers who reported ETS exposure in

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the workplace. The other two studies presented risk estimates which were of borderline statistical significance. Thus, the epidemiologic data are consistent with the null hypothesis, i.e., that there is no association between workplace ETS exposure and nonsmoker lung cancer.

The CIB also purports to review the studies on ETS and heart disease that have appeared since 1986, at which time the Surgeon General remarked that more studies were needed before a conclusion of an association could be made. While additional studies have been published since 1986, taken as a whole, the studies still do not allow a conclusion to be reached.[99] Moreover, the epidemiologic studies on ETS and heart disease may be criticized for several reasons: they use spousal smoking as a surrogate for ETS exposure, they do not have clinical diagnoses of heart disease (e.g., they rely on death certificate data or self-reported symptoms), and they fail to adequately account for confounding factors. The latter include family history of heart disease, blood pressure, serum lipoprotein levels, body mass index, age, menopausal status, dietary fat, alcohol consumption, diabetes and lifestyle factors (e.g., a sedentary lifestyle).

Thus, the NIOSH CIB, which reaches conclusions about purported risks associated with exposure to ETS in the workplace, is not a comprehensive, critical review of the available data.

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of even greater significance, it does not address available workplace data on exposures or potential health effects.

Other Risk Assessments on ETS

Two basic methods (modeling procedures) for estimating the population risk for lung cancer among nonsmokers reporting exposure to ETS have appeared in the scientific literature. The first method, adopted by the U.S. EPA in its Draft Risk Assessment (discussed above), is the Population-Attributable Risk (PAR) approach. A PAR model seeks to establish an estimate of excess risk due to ETS exposure and is expressed as a ratio of the risk assessed for ETS to the total lung cancer risk for nonsmokers from all sources. The PAR is calculated by applying a relative risk estimate associated with reported exposure to ETS (derived from risk rates in epidemiologic studies) to the percentage of individuals believed to be exposed to ETS in the general population.

A second approach used in the literature, called the Extrapolation Method (also called the Linear Extrapolation Method or Dose-Response Extrapolation Model), combines reported risks of lung cancer for active smokers, derived from epidemiologic studies on smokers, with estimates of tobacco smoke exposure (dose) for active smokers. The risk and dose estimates for active smokers are then extrapolated downward to apply to nonsmokers. The

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estimated excess risk for nonsmokers exposed to ETS is obtained by dividing the lung cancer risk reported for active smokers by the ratio between the smokers' and nonsmokers' estimated average exposure to tobacco smoke.

This second approach for estimating excess lung cancer deaths among nonsmokers reportedly due to ETS exposure is exemplified by the model developed by Repace and Lowrey (1985).[100] The authors employed a linear downward extrapolation from the lung cancer risk reported for active smokers (and estimates of tobacco smoke exposure for smokers) to an exposure and residual risk estimate for nonsmokers allegedly exposed to ETS. The model estimated lung cancer mortality among nonsmokers by dividing the reported lung cancer risk for active smokers by a ratio of estimated tobacco smoke exposure for smokers and nonsmokers. The linear dose-extrapolation model therefore requires four estimates:

1. the number of nonsmokers supposedly exposed to ETS;
2. the average ETS exposure of nonsmokers;
3. the average tobacco smoke exposure for active smokers; and
4. the lung cancer risks reported for current active smokers.

Specifically, Repace and Lowrey developed a version of a linear dose-response extrapolation model which is based upon a

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weighted average of nonsmoker exposure to particulates. The weighted average estimate was not derived from actual exposure data but from a model which predicts ambient concentrations of particulate matter from the number of cigarettes smoked in a given volume of air space. The authors also calculated a lung cancer risk estimate and an estimate of daily "tar" (particulate) intake for active smokers. Nonsmoker risk of lung cancer was extrapolated from those estimates to yield 555 lung cancer deaths per year attributable to ETS exposure among nonsmokers.

Arundel, et al., (1987) refined the Repace and Lowrey extrapolation model by replacing Repace and Lowrey's estimates of particulate matter exposure for nonsmokers with actual exposure data from monitoring studies.[101] The Arundel, et al., model also rejected Repace and Lowrey's extrapolation from the dose of active smokers to the exposure of nonsmokers, and replaces the latter with an estimated retained dose of particulates for nonsmokers. Using virtually the same assumptions as Repace and Lowrey, the Arundel et al. model estimates 12 lung cancer deaths per year among 40 million male and female neversmokers.

The various assumptions and estimates employed in the Repace and Lowrey linear dose-extrapolation model have been challenged by a number of scientists.[101-105] One scientist noted that the exposure and dose levels Repace and Lowrey used were not

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based on actual measurements, and that actual measurements reported by other researchers ranged from "ten-to-one-hundred-fold less than that in the Repace and Lowrey model."[102]

Still other scientists have questioned the methods of analysis used in their article.[103-105] For example, the Repace and Lowrey extrapolation model assumes that the carcinogenicity of tobacco smoke depends upon some (unknown) element purportedly located in the particulate phase of ETS. The model also assumes that lung cancer per unit of exposure (i.e., per mg of "tar") is the same for mainstream smoke and ETS, an assumption which is not borne out by the scientific data regarding the chemistry of mainstream smoke and ETS. Moreover, the extrapolation model suggests that the relationship between reported risk and level of exposure is linear (i.e., dose-response), and it assumes that there is no exposure level below which lung cancer risk is absent. The dose-extrapolation model also assumes, with its suggestion of a linear dose-response from active smoking to low level exposure to ETS, that the so-called "one-hit" cancer theory, a theory that one molecule of exposure to a suspected carcinogen is sufficient to induce carcinogenesis, is valid. However, the "one-hit" model has what statisticians call a "zero intercept term," which is equivalent to assuming that lung cancer risk among nonsmokers is zero <u>in the absence of ETS</u>.

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Even with its dubious assumptions and estimates, it is noteworthy that the linear dose-extrapolation model produces estimates of excess lung cancer deaths which are roughly an order of magnitude lower than estimates generated by the PAR model which relies on epidemiologic studies. A number of subsequently published extrapolation models, unlike that of Repace and Lowrey, have been based upon actual data and reasonable estimates of exposure.[101,106-108] These models have been unsuccessful in estimating any appreciable increased risk of lung cancer for nonsmokers reporting exposure to ETS. Indeed, extrapolation models based on estimates of retained particulate matter generate estimates of excess risk which are as much as 20 orders of magnitude lower than estimates generated by the PAR method. Such vast ranges underscore the difference between risk estimates based on epidemiology and those based on dosimetry. This difference is so striking that even the authors of the EPA Draft Risk Assessment were unable to generate a "dose-response based on the extrapolation from mainstream to environmental tobacco smoke," and hence, relied solely upon the PAR model to support their contention of an increased risk of lung cancer among nonsmokers reportedly exposed to ETS.[109]

There have been two published risk assessments of environmental tobacco smoke (ETS) exposure and heart disease, the first by A. Judson Wells in 1988,[110] and the second by Kyle

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Steenland in 1992.[111] However, despite his never having published a risk assessment on ETS and heart disease, Stanton Glantz is the individual most often cited for the conclusion that a large number of annual heart disease deaths in the U.S. are attributable to ETS exposure. In a 1991 article with William Parmley,[112] Glantz claimed that the number of annual ETS-related nonsmoker deaths in the U.S. is approximately 53,000, the largest portion of which (37,000) he claimed was from heart disease.

The figure of 53,000 annual U.S. deaths attributed to ETS exposure originated in a publication by A. Judson Wells in 1988,[110] although Wells actually argued for a "best estimate" of ETS related deaths that was somewhat lower, about 46,000, with 32,000 of these due to heart disease. Stanton Glantz and William Parmley repeated the 53,000 figure in their 1991 article in Circulation. However, they did not themselves independently perform a calculation of "excess" deaths, but instead relied on the earlier work by Wells, which is cited by Glantz and Parmley as the basis for their claim.

To calculate excess deaths due to ETS exposure, Wells used meta-analysis to derive ETS-associated relative risks for lung cancer, heart disease and cancers other than the lung. These relative risks, together with an estimate of the fraction of the population exposed to ETS, were entered into an equation that was used to calculate excess death rates for never smokers. To derive

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a value of actual numbers of deaths related to ETS exposure, these excess death rates were multiplied by the number of people in the U.S. estimated to be exposed. Based on such calculations, Wells estimated that ETS exposure produced 39,000 excess deaths per year in the U.S.

Further calculations attempted to take into account misclassification, either of smokers as nonsmokers or of nonexposed nonsmokers as exposed to ETS. Wells calculated that these adjustments for misclassification resulted in a revision upward of the estimate, from 39,000 to 53,000. Wells then stated that a more "conservative" estimate would be 46,000, a value chosen because it is halfway between the unadjusted value of 39,000 and the adjusted value of 53,000.

It is clear that the claim of 53,000 excess deaths associated with ETS exposure is assailable at every level of its derivation. At the most fundamental level, the studies contributing to the meta-analysis are scientifically flawed. The flaws stem from, among other reasons, small sample sizes, inadequate control for potential confounding factors and unreliable estimates of ETS exposure. Such flaws contribute to the invalidity of the subsequent meta-analysis, a technique which is further called into question because it is not designed to bring together such methodologically disparate studies. Furthermore, any overall estimate of the

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prevalence and levels of ETS exposure within the U.S. is based on assumptions, rather than direct measurement. In addition, a variety of other unproven assumptions are made in attempting to adjust the data to take potential misclassification into account. Finally, the seemingly capricious derivation of the annual death rate claim is reflected in Wells' final calculation in which he decided, based on no particular formula, that the value of 46,000 would be a "best estimate," simply because it was halfway between an unadjusted and adjusted estimate. Such loose and unscientific conclusions should not form a basis for regulatory action.

Kyle Steenland, a National Institute for Occupational Safety and Health employee, also performed a risk assessment of ETS and heart disease, published in 1992.[111] He calculated that 35,000-40,000 annual U.S. heart disease deaths are attributable to ETS exposure. He concluded that "heart disease mortality is contributing the bulk of the public health burden imposed by passive smoking."

There are two important differences between Steenland's estimation process and that used by Wells. First, Steenland did not do a meta-analysis to obtain a pooled estimate of relative risk for heart disease mortality associated with ETS exposure. Instead, he simply adopted the relative risk reported in a single study of a Maryland sample[113] and applied that to the entire U.S.

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population. Second, he focused only on heart disease and did not attempt to calculate ETS-related deaths from other diseases.

Other than the above, Steenland's procedure for calculating deaths attributable to ETS exposure was generally similar to that reported by Wells. This estimation process involved: positing an overall increase in relative risk of heart disease associated with ETS exposure; making adjustments for potential misclassification and for background exposure; estimating the extent of exposure to ETS; and estimating the fraction of nonsmoker heart disease deaths attributable to ETS exposure. These estimates were incorporated into a formula using data on U.S. heart disease death rates and population estimates, from which was derived an estimated number of annual heart disease deaths attributed to ETS exposure. According to Steenland's calculations, "the overall estimate of ETS-attributable heart disease deaths for never-smokers and former smokers is 35000 to 40000." He further commented that these increased risks of death "are higher than those accepted in regulating environmental toxins."

Steenland's calculations involved problems similar to those that plagued Wells' attempt to derive a number of deaths associated with ETS exposure. Although Steenland cannot be criticized for performing an invalid meta-analysis (because he did no meta-analysis at all), his procedure can perhaps be criticized

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even more severely because he took a relative risk based on a single study from a single county in a single state and applied it to the United States as a whole. Criticisms relating to unverified assumptions, which were noted in regard to Wells' calculations, also apply to Steenland's procedure.

Summary

The conclusions of these governmental reports and other publications are extensively relied upon by those who claim that there is a possible association between ETS exposure in the workplace and adverse health effects in nonsmokers. However, these reports and assertions have serious deficiencies that make their conclusions difficult to support. When appropriate scientific scrutiny is exercised, these reports and articles do not provide a defensible basis for the regulation of smoking in the workplace by OSHA.

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PRIMARY EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

Currently, 29 epidemiologic studies examining lung cancer incidence and spousal smoking have been published.[1-29] Tables 1, 2 and 3 list the United States, Asian and European studies, respectively. For purposes of comparison, the relative risks (point estimates) given in the tables are the overall point estimates for spousal smoking reported in the papers. In some cases, the risk in the table was selected from numerous point estimates presented in the paper, based on different definitions of exposure, break-down of the sample by histological type, etc.

Brief synopses and copies of the papers associated with these studies follow this introduction, at Tabs 1 to 29, arranged in chronological order. The copies are highlighted in yellow for useful information and in blue for negative statements.

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United States Studies

Ten of these studies on spousal smoking and lung cancer in nonsmokers (one cohort, nine case-control) were conducted in the United States (Table 1).[3,5,7-9,11,14,16,24,25] None of the relative risks (RR) for spousal smoking reported in these studies is statistically significant. The most recently published paper, that by Janerich, et al., is based upon an unpublished dissertation by Luis Varela.[24] The Janerich, et al., paper discusses a subset of Varela's case-control study, and reports no statistically significant increased risk for spousal smoking, workplace exposure, or exposure in social settings. (It does, however, report a statistically significant increased risk for exposure during childhood (see below).) Overall, the Varela study is important because of its large size and appropriate study design.

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Table 1. United States Studies of Spousal Smoking in Women

Study	Risk Estimate(s)	Comment
Garfinkel, 1981	1.27 (95% CI 0.85-1.89) 1.10 (95% CI 0.77-1.61)	Large cohort study; results contrast with Hirayama
Correa, et al., 1983	2.07 (no CI; n.s.)	Extremely small sample size
Buffler, et al., 1984	0.78 (95% CI 0.34-1.81)	
Kabat and Wynder, 1984	not given	No significant differences between cases and controls regarding ETS exposure at home
Garfinkel, et al., 1985	1.23 (95% CI 0.94-1.60)	Numerous odds ratios presented
Wu, et al., 1985	1.2 (95% CI 0.5-3.3)	Adenocarcinoma only
Brownson, et al., 1987	1.68 (95% CI 0.39-2.97)	Hours per day as exposure category; adenocarcinoma only
Humble, et al., 1987	1.8 (95% CI 0.6-5.4)	
Varela, 1987	numerous	No statistically significant point estimate was presented in 73 different measures of spousal smoking
Janerich, et al., 1990	0.93 (95% CI 0.55-1.57)	Published data for subset of Varela, 1987
Kabat, 1990	0.90 (95% CI 0.46-1.76)	Study in progress; surrogate is "exposed in adulthood at home"

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Asian Studies

In contrast, 13 epidemiologic studies on spousal smoking and lung cancer in nonsmokers (one cohort, twelve case-control) have been conducted in China and Japan (hereafter, "Asian studies") (Table 2).[1,4,10,12,15,17,18,20-22,27,28,29] Of this group, several studies report statistically significant relative risks. However, none of the reported relative risks is greater than 2.5; relative risks under 3.0 have been described as "weak" (see Criticisms section in this notebook). Of particular interest is the 1990 paper by Wu-Williams, et al., conducted in northeastern China.[28] This paper reports a statistically significant negative risk associated with ETS exposure. Other factors (particularly indoor air quality) were reported to be associated with an elevated risk of lung cancer in the Wu-Williams, et al., study; such confounders were not always accounted for in the other Asian studies (see section on Confounders in this notebook).

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Table 2. Asian Studies of Spousal Smoking in Women

Study	Point Estimate(s)	Comment
Hirayama, 1981	2.08 (no CI)	Large cohort study; heavily criticized for improper age-standardization and other flaws
Hirayama, 1984	1.45 (90% CI 1.04-2.02)	Further report on above study
Chan and Fung, 1982	not given	Negative association; suggests more "passive smokers" among controls than cases
Lam, W.K., 1985	not given	Unpublished dissertation; suggests that spousal smoking may be associated with peripheral adenocarcinoma
Akiba, et al., 1986	1.5 (90% CI 1.0-2.5)	Study of atom bomb survivors
Gao, et al., 1987	0.9 (95% CI 0.6-1.4)	"Overall exposure" as surrogate
Koo, et al., 1987	1.64 (95% CI 0.87-3.09)	
Lam, T.H., et al., 1987	1.65 (95% CI 1.16-2.35)	
Geng, et al., 1988	2.16 (95% CI 1.03-4.53)	
Inoue and Hirayama, 1988	2.25 (95% CI 0.91-7.10)	Very small sample size
Shimizu, et al., 1988	1.1 (no CI; n.s.)	Reported statistically significant elevated risks for smoking by case's mother or case's husband's father

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Study	Point Estimate(s)	Comment
Sobue, et al., 1990	0.94 (95% CI 0.62-1.40)	
Wu-Williams, et al., 1990	0.7 (95% CI 0.6-0.9)	Point estimate is statistically significantly negative
Liu, et al., 1991	0.77 (95% CI 0.30-1.96)	Presence of at least one smoker in household used as surrogate

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European Studies

Six studies on spousal smoking and nonsmoker lung cancer were conducted in Europe (Table 3).[2,7,13,19,23,26] Statistical significance was reported in two studies, both by the same research group.[2,26] No major cohort study has yet been conducted in Europe. The cohort studied by Gillis, et al., and Hole, et al., although large, has few lung cancer deaths.[7]

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Table 3. European Studies of Spousal Smoking in Women

Study	Risk Estimate	Comment
Trichopoulos, et al., 1981	2.4 (no CI)	Greece; small case-control study; has been heavily criticized
Trichopoulos, et al., 1983	2.4 (no CI) 3.4 (no CI)	Additional cases and controls added since first paper
Gillis, et al., 1984	not given	Scotland; cohort study; very few lung cancer death (4 cases, 4 controls in women)
Hole, et al., 1989	2.41 (95% CI 0.45-12.83)	Continuation of Gillis, et al., 1984
Lee, et al., 1986	1.00 (95% CI 0.37-2.71)	England
Pershagen, et al., 1987	1.2 (95% CI 0.7-2.1)	Sweden
Svensson, et al., 1989	1.2 (95% CI 0.4-2.9)	Sweden; surrogate is "exposure as adult at home or at work"
Kalandidi, et al., 1990	1.92 (95% CI 1.02-3.59)	Greece; related to Trichopoulos study

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Childhood Exposure to ETS and Adult Lung Cancer in Nonsmokers

When the Janerich, et al., paper was published in 1990, the media focused on a single statistically significant risk ratio (OR) reported by the authors, i.e., an estimated OR of 2.07 (95% CI 1.16-3.68) for "household exposure to 25 or more smoker-years during childhood and adolescence."[24] This OR is the only statistically significant estimate out of 13 exposure categories in the paper. A single statistically significant point estimate could have easily occurred by chance alone in a set of analyses this large.

Only a few other studies have included questions concerning exposure to ETS during childhood, i.e., parental smoking.[5,9,11,12,15,23,25,27] Regarding these studies, Ernst Wynder and Geoffrey Kabat wrote in a 1990 publication:

> No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

(Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.)

Table 4 presents the reported risk estimates from the studies (9 to-date) which discuss childhood ETS exposure and lung

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cancer in nonsmokers. The studies are arranged chronologically in the table. The abbreviation "n.s." stands for "not significant."

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Table 4. Childhood Exposure to ETS and Adult Nonsmoker Lung Cancer Risk

Study	Point Estimate	Statistical Significance
Correa, et al., 1983	not given	n.s.
Garfinkel, et al., 1985		
females	0.91 (95% CI 0.74-1.12)	n.s.
Wu, et al., 1985		
females	0.6 (95% CI 0.2-1.7)	n.s.
Akiba, et al., 1986	not given	n.s.
Gao, et al., 1987		
females	1.1 (95% CI 0.7-1.7)	n.s.
Svensson, et al., 1989		
females, father's smoking	0.9 (95% CI 0.4-2.3)	n.s.
females, mother's smoking	3.3 (95% CI 0.5-18.8)	n.s.
Janerich, et al., 1990		
1-24 smoker/yrs exposure	1.09 (95% CI 0.68-1.73)	n.s.
≥ 25 smoker/yrs exposure	2.07 (95% CI 1.16-3.68)	significantly positive
Kabat, et al., 1990		
males	0.73 (95% CI 0.34-1.59)	n.s.
females	1.68 (95% CI 0.86-3.27)	n.s.
Sobue, et al., 1990		
father's smoking	0.60 (95% CI 0.40-0.91)	significantly negative
mother's smoking	1.71 (95% CI 0.95-3.10)	n.s.
other household members	1.13 (95% CI 0.69-1.87)	n.s.

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Exposure to ETS in the Workplace and Lung Cancer in Nonsmokers

The issue of ETS in the workplace is currently a focus of public interest, as evidenced by the 1990 draft Guide to Workplace Smoking Policies prepared by the United States Environmental Protection Agency. This document is based on the EPA's draft risk assessment, which used data from epidemiologic studies which assessed ETS exposure in terms of spousal smoking, not smoking in the workplace.

The current epidemiologic data on workplace exposures to ETS and lung cancer in nonsmokers are reported in eleven studies which examined workplace exposure via questionnaire.[8,9,11,13,17,22-26,28] None of these studies provides adequate support for an increased risk of lung cancer associated with ETS exposure in the workplace. Only one study reports a single marginally statistically significant risk. The point estimates of the studies (in chronological order) are presented in Table 5. (In the table, "n.s." stands for "not significant.")

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Table 5. Exposure to ETS in the Workplace and Lung Cancer Risk in Nonsmokers

Study	Point Estimate	Statistical Significance
Kabat and Wynder, 1984		
males	18/25 cases vs. 11/25 controls	marginally significant
females	26/53 cases vs. 31/53 controls	n.s.
Garfinkel, et al., 1985		
females, 5 yr exposure	0.88 (95% CI 0.66-1.18)	n.s.
females, 25 yr exposure	0.93 (95% CI 0.73-1.18)	n.s.
Wu, et al., 1985		
females	1.3 (95% CI 0.5-3.3)	n.s.
Lee, et al., 1986	several indices	all n.s.
Koo, et al., 1987		
females	several ORs	all n.s.
Shimizu, et al., 1988		
females	1.2 (no CI given)	n.s.
Svensson, et al., 1989		
females, at home or at work	1.2 (95% CI 0.4-2.9)	n.s.
females, at home and at work	2.1 (95% CI 0.6-8.1)	n.s.
Janerich, et al., 1990		
150 person/yrs exposure	0.91 (95% CI 0.80-1.09)	n.s.
Varela, 1987	27 analyses	all n.s.
Kabat, 1990		
males	0.98 (95% CI 0.46-2.10)	n.s.
females	1.00 (95% CI 0.49-2.06)	n.s.

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Study	Point Estimate	Statistical Significance
Kalandidi, et al., 1990 females	1.08 (95% CI 0.24-4.87)	n.s.
Wu-Williams, et al., 1990 females	1.1 (95% CI 0.9-1.6)	n.s.

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EPIDEMIOLOGIC STUDIES INCLUDING ESTIMATES OF WORKPLACE ETS EXPOSURE AND LUNG CANCER RISK IN NONSMOKERS

Study	Point Estimate & 95% CI	Reference
1. Brownson, et al., 1992		
• "highest quartile" of exposure		
females	1.2 (0.9-1.7)(n.s.)	from publication
2. Butler, 1988		
• worked with a smoker for 11+ years		
females	1.47 (0.15-14.06)(n.s.)	LeVois & Layard, 1992
males	0.0	
3. Fontham, et al., 1991		
• ever exposed		
females	1.34 (1.03-1.73)	from publication; LeVois & Layard, 1992
4. Garfinkel, et al., 1985		
• exposure in last 25 years		
females	0.88 (0.66-1.18)(n.s.)	from publication; Lee, 1992; LeVois & Layard, 1992
5. Janerich, et al., 1990		
• 150 person-years exposure		
both	0.91 (0.80-1.04)(n.s.)	from publication; Lee, 1992; LeVois & Layard, 1992

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Study	Point Estimate & 95% CI	Reference
6. Kabat & Wynder, 1984		
• current regular exposure		
females	26/53 cases v. 31/53 controls	from publication
	0.68 (0.32-1.47)(n.s.)	Lee, 1992; LeVois & Layard, 1992
males	18/25 cases v. 11/25 controls	from publication
	3.27 (1.01-10.6)	Lee, 1992
	3.27 (1.01-10.61)	LeVois & Layard, 1992
7. Kabat, 1990		
• ever exposed		
females	1.00 (0.49-2.06)(n.s.)	from publication; Lee, 1992; LeVois & Layard, 1992
males	0.98 (0.46-2.10)(n.s.)	from publication; Lee, 1992; LeVois & Layard, 1992
8. Kalandidi, et al., 1990		
• "between extreme quartiles"		
females	1.08 (0.24-4.87)(n.s.)	from publication
• some v. minimal exposure		
females	1.70 (0.69-4.18)(n.s.)	Lee, 1992
• exposed at work		
females	1.39 (0.76-2.54)(n.s.)	LeVois & Layard, 1992

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Study	Point Estimate & 95% CI	Reference
9. Koo, et al., 1984		
• exposed at workplace		
females	0.91 (not given)(n.s.)	from publication; (1987 paper more commonly used)
10. Lee, et al., 1986		
• ever exposed		
females	0.63 (0.17-2.33)(n.s.)	Lee, 1992; LeVois & Layard, 1992
males	1.61 (0.39-6.60)(n.s.)	Lee, 1992: LeVois & Layard, 1992
11. Shimizu, et al., 1988		
• someone at workplace smokes		
females	1.2 (not given)(n.s.)	from publication
	1.2 (0.70-2.04)	Lee, 1992
	1.2 (0.69-2.01)	LeVois & Layard, 1992
12. Stockwell, et al., 1992		
• exposure at work		
females	"no statistically significant increase in risk"	from publication
13. Wu, et al., 1985		
• exposed at work		
females	1.3 (0.5-3.3)(n.s.)	from publication; Lee, 1992; LeVois & Layard, 1992

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Study	Point Estimate & 95% CI	Reference
14. Wu-Williams, et al, 1992		
• exposed at work		
females	1.1 (0.9-1.6)(n.s.)	from publication
	1.22 (0.95-1.57)	Lee, 1992
	1.1 (0.86-1.41)	LeVois & Layard, 1992

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RESULTS OF META-ANALYSES

Lee, 1992[1]

- used nine studies
  (did not include Brownson, et al., 1992; Butler, 1988; Fontham, et al., 1991; Koo, et al., 1984; Stockwell, et al., 1992)
- data for males and females combined
- summary RR = 0.98 (0.89-1.08)(n.s.)

LeVois and Layard, 1991[2]

- used 11 studies
  (did not include Brownson, et al., 1992; Koo, et al., 1984; Stockwell, et al., 1992)
- data for males and females combined
- summary RR = 1.01 (0.92-1.11)(n.s.)

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STUDY[7]	NO. OF CASES	OR	95% CI	USED BY EPA
Lam, 1985	163[8]	--	-- (SS)[5]	*
Lee, et al., 1986	22	1.0	(0.37-2.71)	*
Liu, et al., 1991	45	0.74	(0.30-1.96)	*
Pershagen, et al., 1987	67	1.2	(0.7-2.1)	*
Shimizu, et al., 1988	90	1.1	(NS)[4]	*
Sobue, et al., 1990	64	0.94	(0.62-1.40)	*
Stockwell, et al., 1992	210[8]	1.6	(0.8-3.0)	
Svensson, et al., 1989	17	1.20	(0.4-2.9)	*
Trichopoulos, et al., 1983	38	2.4	-- (SS)[5]	*
Wu, et al., 1985	29	1.2	(0.5-3.3)	*
Wu-Williams, et al., 1990	205	0.7	(0.6-0.9)	*

1. Number of nonsmoking lung cancer cases married to smokers, and used in spousal smoking analysis.

2. Odds ratio for overall index of spousal smoking, as reported in original publication.

3. 90% CI, as reported in original publication.

4. OR and/or CI not given; reportedly not statistically significant (NS).

5. Statistically significant (SS).

6. Data are for males and females combined.

7. Some also reference Katada, et al., 1988; the study provides insufficient data to calculate an OR, but is reportedly not statistically significant.

8. Total number of cases; numbers not given for individual analyses.

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STUDIES OF SPOUSAL SMOKING AND LUNG CANCER IN NONSMOKING WOMEN

STUDY	NO. OF CASES[1]	OR[2]	95% CI	USED BY EPA
Akiba, et al., 1986	73	1.5	(1.0-2.5)[3]	*
Brownson, et al., 1987	10	1.68	(0.39-2.97)	*
Brownson, et al., 1992	218	1.0	(0.8-1.2)	
Buffler, et al., 1984	33	0.78	(0.34-1.81)	*
Butler, 1988	4	2.04	(0.54-7.65)	*
Chan & Fung, 1982	34	--	(NS)[4]	*
Correa, et al., 1983	14	2.07	(NS)[4]	*
Fontham, et al., 1991	264	1.21	(0.96-1.54)	*
Gao, et al., 1987	189	0.9	(0.6-1.4)	*
Garfinkel, 1981	88	1.27	(0.85-1.89)	*
Garfinkel, et al., 1985	134	1.22	(0.97-1.71)	*
Geng, et al., 1988	34	2.16	(1.03-4.53)(SS)[5]	*
Hirayama, 1984	163	1.45	(1.04-2.02)[3](SS)[5]	*
Hole, et al., 1989[6]	5	2.41	(0.45-12.83)	*
Humble, et al., 1987[6]	16	1.8	(0.6-5.4)[3]	*
Inoue & Hirayama, 1988	28	2.25	(0.91-7.10)	*
Janerich, et al., 1990[6]	129	0.93	(0.55-1.57)	*
Kabat & Wynder, 1984	13	--	(NS)[4]	*
Kabat, 1990	35	0.90	(0.46-1.76)	
Kalandidi, et al., 1990	91	2.11	(1.09-4.08)(SS)[5]	*
Koo, et al., 1987	51	1.64	(0.87-3.09)	*
Lam, et al., 1987	115	1.65	(1.16-2.35)(SS)[5]	*

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UNITED STATES STUDIES OF SPOUSAL SMOKING
AND LUNG CANCER IN NONSMOKING WOMEN

USED BY EPA

STUDY	NO. OF CASES[1]	OR[2]	95% CI
Brownson, et al., 1987	10	1.68	(0.39-2.97)
Buffler, et al., 1984	33	0.78	(0.34-1.81)
Butler, 1988	4	2.04	(0.54-7.65)
Correa, et al., 1983	14	2.07	(NS)[3]
Fontham, et al., 1991	264	1.21	(0.96-1.54)
Garfinkel, 1981	88	1.27	(0.85-1.89)
Garfinkel, et al., 1985	134	1.22	(0.97-1.71)
Humble, et al., 1987[4]	16	1.8	(0.6-5.4)[5]
Janerich, et al., 1990[4]	129	0.93	(0.55-1.57)
Kabat & Wynder, 1984	13	--	(NS)[3]
Wu, et al., 1985	29	1.2	(0.5-3.3)

1. Number of nonsmoking lung cancer cases married to smokers, and used in spousal smoking analysis.

2. Odds ratio for overall index of spousal smoking, as reported in original publication.

3. OR and/or CI not given; reportedly not statistically significant (NS).

4. Data are for males and females combined.

5. 90% CI, as reported in original publication.

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NOT USED BY EPA

STUDY	NO. OF CASES	OR	95% CI
Brownson, et al., 1992	218	1.0	(0.8-1.2)
Kabat, 1990	35	0.90	(0.46-1.76)
Stockwell, et al., 1992	210[6]	1.6	(0.8-3.0)

6. Total number of cases; numbers not given for individual analyses.

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BROWNSON, R.C., ALAVANJA, M.C.R., HOCK, E.T., AND LOY, T.S. "PASSIVE SMOKING AND LUNG CANCER IN NONSMOKING WOMEN," AMERICAN JOURNAL OF PUBLIC HEALTH 82: 1525-1530, 1992

This case-control study is among the largest conducted on reported ETS exposure and lung cancer incidence. It includes 432 "lifetime" nonsmokers and 186 exsmokers, and 1,402 controls. Cases were identified from 1986-1991 through the Missouri Cancer Registry. Interviews were conducted by telephone; 402 surrogate interviews were conducted among the 618 cases. ETS exposure was assessed as duration, intensity, and hours per day of exposure ("quantitative measures") and as "perceived" levels of exposure. No statistically significant odds ratios (ORs) were reported for any of the "quantitative" measures of exposure. Nevertheless, the authors concluded that their data supported a "small but consistent elevation in the risk of lung cancer in nonsmokers due to passive smoking." Moreover, they proposed that "[t]he proliferation of . . . regulations that restrict smoking in public places and work sites is well founded."

- An OR of 1.0 (95% CI 0.8-1.2) was reported for spousal smoking in nonsmokers (218 cases and 598 controls). This odds ratio is not statistically significant.

- For exposure during childhood, no statistically significantly elevated risk estimates were reported. However, for parents having ever smoked, an OR of 0.7 (95% CI 0.5-0.9) was reported, based on 74 cases and 289 controls; this particular OR was statistically significantly negative.

- The authors wrote that, based on their data, "there was no elevated lung cancer risk associated with passive smoke exposure in the workplace." However, the data on reported workplace exposures were not presented.

- More than 80 ORs were reported in this study. The large number of subgroup analyses, sometimes referred to as "data-dredging," increases the probability that some statistically significant ORs will be reported due to chance alone.

- While no statistically significant ORs were reported for the quantitative indices of exposure, a few were reported for the indices of perceived exposure.

- No statistically significant ORs were calculated when the data were analyzed by lung cancer cell type, further contributing to inconsistencies in this area.

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- The authors state that their study has "several major strengths," citing large sample size, high response rates from cases and controls and pathology review for cases. While the sample size is indeed large, surrogate respondents accounted for 65% of case interviews, and histological confirmation was unavailable for approximately one-fourth of the cases.

- Reportedly, the potential confounders of age, smoking history, history of previous lung disease, dietary beta-carotene consumption, and dietary fat consumption were considered. The authors reported that only age, active smoking (for exsmokers), and previous lung disease "appeared to confound passive smoking findings."

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Passive Smoking and Lung Cancer in Nonsmoking Women

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ABSTRACT

Objectives. The causes of lung cancer among nonsmokers are not clearly understood. To further evaluate the relation between passive smoke exposure and lung cancer in nonsmoking women, we conducted a population-based, case-control study.

Methods. Case patients (n = 618), identified through the Missouri Cancer Registry for the period 1986 through 1991, included 432 lifetime nonsmokers and 186 ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year. Control subjects (n = 1402) were selected from driver's license and Medicare files.

Results. No increased risk of lung cancer was associated with childhood passive smoke exposure. Adulthood analyses showed an increased lung cancer risk for lifetime nonsmokers with exposure of more than 40 pack-years from all household members (odds ratio [OR] = 1.3; 95% confidence interval [CI] = 1.0, 1.8) or from spouses only (OR = 1.3; 95% CI = 1.0, 1.7). When the time-weighted product of pack-years and average hours exposed per day was considered, a 30% excess risk was shown at the highest quartile of exposure among lifetime nonsmokers.

Conclusions. Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. Comprehensive actions to limit smoking in public places and worksites are well-advised. (*Am J Public Health.* 1992;82:1525–1530)

Introduction

Although most lung cancer occurs in smokers, approximately 9% to 13% of lung cancer cases in US women develop in lifetime nonsmokers.[1-5] The causes of lung cancer in nonsmokers have not been widely studied, but probably comprise a diverse set of factors including genetics, occupational factors, radon exposure, diet, and a history of nonmalignant lung disease.

In addition to these risk factors, the etiologic role of passive smoke exposure has received increasing scrutiny over the past decade. Numerous studies[5-20] have suggested an elevation in lung cancer risk for nonsmoking females who live with a smoker, with a summary excess risk of approximately 30%.[21,22] However, several recent studies[1,23-27] have shown no increased lung cancer risk due to spousal smoking.

Limited evidence[7,26] also suggests that exposure to passive smoke in childhood may increase risk of lung cancer. For example, a recent case-control study from New York found that household exposure to tobacco smoke during childhood of 25 or more smoker-years' duration was associated with a doubling of lung cancer risk.[26]

Most previous studies of passive smoking and lung cancer, although suggestive of a positive effect, have had several deficiencies. These deficiencies include sample sizes insufficient to singly demonstrate significant elevations in risk, limited data on passive smoke exposure in both childhood and adulthood, and lack of histologic review of cases to verify lung cancer diagnosis and to allow analyses by cell type.

To more fully evaluate the relationship between lung cancer and passive smoke exposure in childhood and adulthood, we conducted a large case-control study of lung cancer among nonsmoking women.

Methods

Case Group

Case patients were identified through the Missouri Cancer Registry, which is maintained by the Missouri Department of Health. The Registry began collecting data on incident cancer cases from public and private hospitals in 1972, and hospital reporting was mandated by law in 1984. Registry reporting procedures have been discussed in more detail elsewhere.[28] To ensure complete reporting of lung cancer cases in women for the current study, we had Registry staff complete special case ascertainment visits to participating hospitals. The case series included White Missouri women, aged 30 to 84 years, who were diagnosed with primary lung cancer between January 1986 and June 1991. Selection was limited to Whites because of small numbers of other racial/ethnic

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This paper was submitted to the Journal February 19, 1992, and accepted with revisions August 12, 1992.

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groups. The case group included both lifetime nonsmokers and ex-smokers who had stopped smoking at least 15 years before diagnosis or who had smoked for less than 1 pack-year. From the 3475 cases of lung cancer in women reported for the study period, 650 eligible patients were identified. Physicians denied interview permission for 24 (4%) of these patients and an additional 8 women (1%) refused to be interviewed. The final case group included 432 (70%) lifetime nonsmokers and 186 (30%) ex-smokers. Of the 618 case interviews, 216 were conducted with patients themselves and 402 were conducted with surrogates because the patient was too ill to be interviewed or had died. Of the surrogate interviews, 105 (26%) were conducted with the patient's spouse and 297 (74%) were conducted with another relative (e.g., offspring or sibling).

Histologic Confirmation of Cases

Tissue slides were reviewed for histologic verification for 468 (76%) of the 618 cases. Slides for these cases were examined simultaneously by three pathologists (T.L., E.I., and J.M.) using a multiheaded microscope without knowledge of the referring pathologist's diagnosis. In surgical specimens, consensus diagnoses were obtained with the criteria outlined in the World Health Organization classification scheme.[29] When only cytologic material was available, consensus was obtained with standard cytologic criteria.[30]

Control Group

A population-based sample of control subjects was ascertained by two methods. For women younger than 65 years, a sample of state driver's license files was provided by the Missouri Department of Revenue. For women aged 65 to 84 years, control subjects were generated from the Health Care Finance Administration's roster of Medicare recipients.[31] On the basis of age distribution of lung cancer cases previously reported to the Registry, the final control group was matched by age group to case patients at an approximate 2.2 to 1 ratio. All control subjects were interviewed directly. Of the 1862 potentially eligible control subjects, 335 (18%) refused the initial screening interview and 125 (7%) of those screened and found eligible refused the full interview. The final control group numbered 1402.

Questionnaire Design and Administration

Telephone interviews were conducted by trained interviewers. The first phase of the interview consisted of a screening questionnaire to verify the age, race, and smoking status of case patients and control subjects. For subjects who were screened and found eligible and who agreed to the full interview, the study questionnaire consisted of sections on residential history, passive smoke exposure, personal health history, family health history, reproductive history, occupational exposure, and dietary factors.

Questions regarding passive smoking focused on exposure in both childhood (17 years and younger) and adulthood (18 years and older). For each time period, respondents were questioned about the source of exposure (e.g., a parent or spouse). After an individual source was determined, a series of detailed questions were asked on the type of tobacco used, duration of exposure, intensity of exposure, and average number of hours per day exposed. These questions were partially modeled after those developed by Wynder et al.[32] In addition to quantitative estimates of exposure, respondents were asked to estimate a perceived level of exposure during childhood and adulthood ("During most of your adult years, would you say that your average exposure to smoke at home was light, moderate, or heavy?").

Analyses

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with multiple logistic regression.[33] The linearity of trends in risk according to level of passive smoke exposure was evaluated with Mantel's one-tailed test.[34] We initially examined numerous potential confounding factors. These included age, active smoking (for ex-smokers), history of previous lung diseases, dietary beta carotene, and dietary fat. Of these variables, only age, active smoking, and previous lung disease appeared to confound passive smoking findings; therefore, the results presented are adjusted for these factors.

Histologic type-specific analyses were conducted for cases for which consensus diagnoses were determined. These analyses were undertaken because earlier studies[5,18,20] have shown variations in risk by cell type, and biological mechanisms have been proposed that might account for these variations.[20,35]

Results

Sociodemographic and smoking-related characteristics of case patients and control subjects have been presented in detail elsewhere.[36] In brief, the average ages of case patients and control subjects were 71.5 years and 69.9 years, respectively. The two groups were also comparable on level of education and income. Among ex-smokers, the median interval since cessation was 24 years, and average smoking intensity was 16.4 cigarettes per day.

There was little evidence of increased lung cancer risk associated with passive smoke exposure in childhood (Table 1). This lack of association was apparent for both the dichotomous variables (never vs ever exposed) and quantitative measures such as pack-years. The only suggestion of elevated risk was noted for less quantitative exposure variables (not shown in table). Among lifetime nonsmokers, an increased risk of lung cancer was shown for those reporting moderate (OR = 1.7; 95% CI = 1.1, 2.5) and heavy (OR = 2.4; 95% CI = 1.3, 4.7) exposure to passive smoke in childhood. Risk estimates for most childhood exposure variables were slightly higher (approximately 20% to 30%) when analyses included only direct interviews, although none achieved statistical significance.

An elevated risk of lung cancer was identified for lifetime nonsmokers at the highest quartile of passive smoke exposure in adulthood (Table 2). At an exposure level of more than 40 pack-years, lifetime nonsmokers showed a 30% increase in risk whether the source of exposure was all household members or spouses only. Similarly, when the product of pack-years and average number of hours exposed per day was considered, lung cancer risk for lifetime nonsmokers was elevated for the highest exposure quartile whether the source was all household members (OR = 1.3; 95% CI = 1.0, 1.8) or spouses only (OR = 1.3; 95% CI = 1.0, 1.7). Among lifetime nonsmokers, a positive increasing trend in risk was noted for pack-years (P = .06). Passive smoking–related risk estimates for adulthood exposures were slightly lower for all subjects (i.e., both ex-smokers and lifetime nonsmokers) than for lifetime nonsmokers alone, although the same general elevations in risk were noted. When analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent. Regarding less quantitative exposure variables, elevated risk was shown for all subjects (OR = 1.7; 95% CI = 1.1, 2.6) and for lifetime nonsmok-

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TABLE 1—Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) for the Relationship between Passive Smoke Exposure during Childhood and Lung Cancer in Women, Missouri, 1986 through 1991

Source of Exposure	All Subjects[b]				Lifetime Nonsmokers			
	No. Cases	No. Controls	OR	95% CI	No. Cases	No. Controls	OR	95% CI
All household members								
Never	430	928	1.0		323	802	1.0	
Ever	185	472	0.8	0.7, 1.1	106	364	0.8	0.6, 1.1
Cigarette pack-years								
0	430	928	1.0		323	802	1.0	
>0–15	42	129	0.7	0.5, 1.0	27	104	0.7	0.4, 1.1
>15–25	31	119	0.6	0.4, 0.9	20	91	0.6	0.4, 1.0
>25	34	117	0.7	0.4, 1.1	21	87	0.7	0.4, 1.2
Parents only								
Never	489	1021	1.0		357	877	1.0	
Ever	126	379	0.7	0.5, 0.9	74	289	0.7	0.5, 0.9
Cigarette pack-years								
0	489	1021	1.0		357	877	1.0	
>0–15	19	90	0.4	0.3, 0.7	12	70	0.5	0.2, 0.8
>15–25	27	118	0.5	0.3, 0.7	17	87	0.5	0.3, 0.9
>25	33	99	0.7	0.5, 1.1	21	74	0.8	0.5, 1.4

[a]Adjusted for age, history of previous lung disease, and active smoking (all subjects only).
[b]Includes lifetime nonsmokers and ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year.

ers (OR = 1.8; 95% CI = 1.1, 2.9) who reported heavy exposure to passive smoke.

In general, there was no elevated lung cancer risk associated with passive smoke exposure in the workplace (not shown in table). Only lifetime nonsmokers showed a slight increase in risk at the highest quartile of workplace exposure (OR = 1.2; 95% CI = 0.9, 1.7).

Among the 468 lung cancers that were verified histologically, the predominant cell types were adenocarcinoma (62.4%), other/mixed cell types (25.2%), squamous cell carcinoma (5.8%), bronchioalveolar carcinoma (4.1%), and small cell carcinoma (2.5%). The other/mixed cell type category consisted mainly of large cell lung cancers, though these lacked sufficient pathologic evidence for precise classification. Table 3 presents results of cell type–specific analyses for adulthood exposures. Elevated risk was shown for other/mixed cell types at more than 40 pack-years of exposure (OR = 1.6; 95% CI = 1.0, 2.5). Although it was based on small numbers, a risk estimate of 1.7 was observed for small cell carcinoma at the highest level of exposure.

We also examined risk among women who had been exposed to passive smoke in both childhood and adulthood, in childhood but not in adulthood, and in adulthood but not in childhood. There was no evidence of interaction between exposure during the two periods.

Discussion

Our study suggests that exposure to high levels of environmental tobacco smoke in adulthood increases the risk of lung cancer in nonsmokers. Exposure of more than 40 pack-years' duration increased the risk of lung cancer among nonsmokers by approximately 30%. This relationship was consistently demonstrated among lifetime nonsmokers whether the exposure variable was pack-years or the time-weighted product of pack-years and average number of hours exposed per day. Our findings are similar to those of another large study of lung cancer in nonsmoking women[20] that identified an OR of approximately 1.3 due to exposure to greater than 40 pack-years of spousal smoking.

In earlier studies, the most commonly reported index of passive smoking exposure has been the presence or absence of a smoking spouse. In our data set, no elevated risk was noted for this variable. Since our study was limited to women, part of the difference between our findings and those of earlier studies may be due to differences in the effects of passive smoke exposure by gender. The National Research Council's summary of 13 studies[21] found overall relative risks of lung cancer in nonsmokers due to spousal smoking of 1.32 for women and 1.62 for men (although the estimate for men was based on few cases). It is possible that men are exposed to other factors (e.g., occupational exposures) that may interact with passive smoke exposure to increase risk above that observed in women. Presence or absence of a smoking spouse is a relatively crude measure of passive smoke exposure, with a potential for wide variability in actual exposure. It was noted in one survey, for example, that 47% of women married to smokers reported zero hours of passive smoke exposure at home.[37] It has also been shown that considering spousal exposure alone may underestimate total household passive smoke exposure.[38] Another factor that may account for the differences in lung cancer risk due to spousal smoking between our study and earlier studies may be time trends in smoking patterns. The declining prevalence of smoking among men[39] has probably resulted in decreasing years and perhaps levels of exposure to passive smoke in the home among nonsmoking women whose husbands smoke.

Contrary to the findings of two earlier case-control studies,[7,26] our data showed no evidence of excess lung cancer risk due to passive smoke exposure in childhood. The risk of lung cancer due to childhood passive smoking may have some analogy to risk among ex-smokers. After 10 years of abstinence, the lung cancer risk for ex-smokers declines to 30% to 50% of the risk for continuing smokers.[40] Similarly, lung cancer risk due to passive smoke exposure in childhood may decline by adulthood, especially in the absence of adult-

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TABLE 2—Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) for the Relationship between Passive Smoke Exposure during Adulthood and Lung Cancer in Women, Missouri, 1986 through 1991

Source of Exposure	All Subjects[b]				Lifetime Nonsmokers			
	No. Cases	No. Controls	OR	95% CI	No. Cases	No. Controls	OR	95% CI
All household members								
Never	221	527	1.0		170	470	1.0	
Ever	394	873	1.0	0.8, 1.2	261	696	1.1	0.8, 1.3
Cigarette pack-years								
0	221	527	1.0		170	470	1.0	
>0–15	88	234	0.9	0.6, 1.2	56	181	0.9	0.6, 1.2
>15–40	91	261	0.8	0.6, 1.0	62	199	0.9	0.6, 1.2
>40	146	264	1.3	1.0, 1.6	107	217	1.3	1.0, 1.8
Cigarette pack-years × hours/day[c]								
0	221	527	1.0		170	470	1.0	
>0–50	90	261	0.8	0.6, 1.1	63	206	0.9	0.6, 1.2
>50–175	89	246	0.8	0.6, 1.1	58	189	0.9	0.6, 1.2
>175	124	238	1.2	0.9, 1.6	92	192	1.3	1.0, 1.8
Spouse only								
Never	287	650	1.0		213	568	1.0	
Ever	328	750	0.9	0.8, 1.1	218	598	1.0	0.8, 1.2
Cigarette pack-years								
0	287	650	1.0		213	568		
>0–15	58	166	0.7	0.5, 1.0	32	128	0.7	0.5, 1.1
>15–40	81	258	0.7	0.5, 0.9	54	200	0.7	0.5, 1.0
>40	150	266	1.2	0.9, 1.5	110	216	1.3	1.0, 1.7
Cigarette pack-years × hours/day[c]								
0	287	650	1.0		213	568	1.0	
>0–50	64	201	0.7	0.5, 0.9	41	161	0.7	0.5, 1.0
>50–175	81	237	0.7	0.5, 1.0	52	183	0.8	0.5, 1.1
>175	126	241	1.1	0.9, 1.5	94	193	1.3	1.0, 1.7

[a]Adjusted for age, history of previous lung disease, and active smoking (all subjects only).
[b]Includes lifetime nonsmokers and ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year.
[c]The product of total pack-years and average number of hours exposed per day to passive smoke in the home.

TABLE 3—Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) for the Relationship between Passive Smoke Exposure during Adulthood and Lung Cancer in Women, by Histologic Type, Missouri, 1986 through 1991

Source of Exposure	Adenocarcinoma			Other/Mixed			Squamous Cell			Small Cell		
	No. Cases	OR	95% CI	No. Cases	OR	95% CI	No. Cases	OR	95% CI	No. Cases	OR	95% CI
All household members												
Never	100	1.0		37	1.0		10	1.0		3	1.0	
Ever	192	1.1	0.8, 1.5	80	1.2	0.8, 1.8	16	0.7	0.3, 1.7	9	1.2	0.3, 4.5
Cigarette pack-years												
0	100	1.0		37	1.0		10	1.0		3	1.0	
>0–15	49	1.1	0.8, 1.6	17	1.0	0.5, 1.7	4	0.7	0.2, 2.2	1	0.5	0.0, 4.8
>15–40	48	0.9	0.6, 1.4	18	0.8	0.5, 1.6	5	0.7	0.2, 2.0	2	0.8	0.1, 4.8
>40	61	1.2	0.8, 1.7	31	1.5	0.9, 2.6	2	0.3	0.1, 1.4	5	2.2	0.5, 9.7
Spouse only												
Never	131	1.0		48	1.0		14	1.0		4	1.0	
Ever	161	1.0	0.8, 1.3	69	1.1	0.7, 1.7	12	0.6	0.3, 1.3	8	1.2	0.3, 4.1
Cigarette pack-years												
0	131	1.0		48	1.0		14	1.0		4	1.0	
>0–15	36	1.0	0.7, 1.6	10	0.7	0.4, 1.5	3	0.7	0.2, 2.4	1	0.7	0.1, 6.6
>15–40	41	0.8	0.5, 1.1	16	0.8	0.4, 1.4	6	0.8	0.3, 2.1	3	1.2	0.3, 5.6
>40	62	1.1	0.8, 1.5	34	1.6	1.0, 2.5	2	0.2	0.1, 1.1	4	1.7	0.4, 7.0

[a]Adjusted for age, history of previous lung disease, and active smoking.

hood exposure. In addition, there may be low reliability for quantitative measures (intensity and duration) of passive smoke exposure in childhood,[41,42] which makes assessment of lung cancer risk due to passive smoke exposure in childhood particularly difficult. Reliability and validity of measures of childhood exposure may be especially problematic when a large percentage of surrogate interviews are conducted (as in our study). Partially because of these limitations, few studies of child-

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hood passive smoking and lung cancer have been conducted, and further research in this area is needed.

Our analyses by histologic type showed the largest increase in risk for other/mixed cell types and, although the estimate was based on very small numbers, for small cell carcinoma. Previous studies are inconsistent and often lacking in sample size when evaluating risk by cell type. Garfinkel et al.[10] found an elevated risk for squamous cell carcinoma and for other/mixed cell types. Others[5,18] have observed larger elevations for squamous and small cell carcinoma than for adenocarcinoma. In contrast, Wu et al.[11] and Fontham et al.[20] found larger increases for adenocarcinoma. An additional difficulty in evaluating previous studies of passive smoking and lung cancer by histologic type is that few studies have conducted systematic pathology reviews to verify cell type.

Our study has several major strengths. These include the large sample size—one of the largest series of nonsmoking lung cancer cases to date. In addition, we had relatively high response rates from both case patients and control subjects. Finally, we conducted a pathology review of cases.

The main limitation of our study is the possibility of recall bias for passive smoke exposure variables. The less quantitative measures of passive exposure (i.e., light, moderate, or heavy exposure) resulted in larger risk estimates than more quantitative estimates such as pack-years. Because there is no way to confirm previous passive smoke exposure, it is difficult to determine the best index for estimating exposure. However, we found that lung cancer risk due to adulthood passive smoke exposure was elevated at the highest quartile of exposure whether we used a more quantitative (e.g., pack-years) or less quantitative (e.g., heavy exposure) variable.

Another possible source of bias in our study is the large number of surrogate interviews for cases. Earlier studies,[38,43] however, have shown relatively close agreement on most passive smoke exposure variables as reported by subjects and spouses. We found fairly minor alterations in risk estimates when analyses were restricted to directly interviewed cases. In addition, we compared sociodemographic characteristics of direct and surrogate case-group interviews and found close agreement for most variables. As one might expect, the exception was age; there was a tendency toward more younger case patients in direct interviews.

In summary, our study and others conducted during the past decade suggest a small but consistent elevation in the risk of lung cancer in nonsmokers due to passive smoking. The proliferation of federal, state, and local regulations that restrict smoking in public places and work sites[44] is well founded. □

Acknowledgments

This study was supported in part by National Cancer Institute contracts NO1-CP7-1096-01 and NO1-CP7-1096-02.

The authors gratefully acknowledge the assistance of numerous individuals and organizations who made this study possible: Sandi Ezrine, Patsy Henderson, Joan Huber, and other staff of Survey Research Associates, Inc, for valuable help in all phases of the study; Dr. Jian Chang, Carlene Anderson, Debbie Pinney, and Jeanie Shanebarger of the Missouri Cancer Registry, Missouri Department of Health, for assistance in data collection and patient tracking; Dr. Ellis Ingram of the University of Missouri School of Medicine and Dr. Jeffrey Meyers of the Mayo Clinic for their assistance in reviewing pathology slides; Drs. William Blot and Jay Lubin of the National Cancer Institute for helpful comments on the manuscript; and the Missouri Department of Revenue and the Health Care Finance Administration for their help in selecting population-based controls.

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STOCKWELL, H.G., GOLDMAN, A.L., LYMAN, G.H., NOSS, C.I., ARMSTRONG, A.W., PINKHAM, P.A., CANDELORA, E.C., AND BRUSA, M.R., "ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER RISK IN NONSMOKING WOMEN," JOURNAL OF THE NATIONAL CANCER INSTITUTE 84: 1417-1422, 1992

This case-control study, conducted in central Florida, included 210 nonsmoking female lung cancer cases and 301 controls. Nonsmokers were defined as having smoked for a total of less than six months or having smoked less than 100 cigarettes in one's lifetime. Interviews were conducted either in person or via telephone. More than two-thirds of the interviews were conducted with surrogate respondents; approximately 44% were with surrogates other than the cases' husbands. The authors reported several statistically significant ORs: for the highest categories of exposure, for lung cancer cell types other than adenocarcinoma, and for exposure estimates based on responses by cases and their husbands. However, many ORs, including the overall estimate for spousal smoking, were not statistically significant. Nevertheless, the authors concluded that "long-term exposure to environmental tobacco smoke increases the risk of lung cancer in women who are nonsmokers."

- Based on a yes/no definition of exposure, an odds ratio for spousal smoking of 1.6 (95% CI 0.8-3.0) was reported. The numbers of cases and controls used in calculating this risk estimate were not presented.

- Odds ratios were also calculated for reported exposure from parents and siblings during childhood. Statistically significant odds ratios were reported for the highest index of exposure, namely, 22 or more smoke-years (the sum of reported years of exposure to cigarette smoke from each smoker in the household).

- The authors wrote: "We found no statistically significant increase in risk associated with exposure to environmental tobacco smoke at work." However, they failed to present the data on this index of exposure.

- Adenocarcinoma accounted for 61% of the cases in this study. When the data were analyzed by lung cancer cell type, no relative risk higher than 2.0, and no statistically significant relative risk, was reported for adenocarcinoma. These data thus contrast with the recent Fontham, et al., study, which reported elevated ORs for adenocarcinoma.

- More than 80 risk estimates were presented in this study; "data-dredging" is thus evident.

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The authors do not indicate the numbers of cases and controls associated with the multitude of ORs presented. It is not possible to determine whether the same subgroup of cases was the basis for all the reported statistically significant risk estimates.

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REPORTS

Environmental Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women

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Background: Exposure to environmental tobacco smoke (passive smoking) has been suggested to be a cause of lung cancer, although early epidemiologic studies have produced inconsistent results. *Purpose*: We conducted an epidemiologic case-control study to assess the relationship between exposure to environmental tobacco smoke and lung cancer risk among women who have never smoked (i.e., having smoked for a total of <6 months or having smoked <100 cigarettes in their lifetimes). *Methods*: Case patients (n = 210) were women with histologically confirmed primary carcinomas of the lung who were lifetime nonsmokers. They were identified through hospital tumor registries and the Florida Cancer Data System of the Statewide Cancer Registry. Community-based control women (n = 301) were also lifetime nonsmokers and were identified through random-digit dialing. Details on childhood and adulthood exposures to environmental tobacco smoke were ascertained through interviews with the study participants themselves or with surrogate respondents. Risks were calculated in terms of smoke-years, defined as the sum of the reported years of exposure to cigarette smoke from each smoker in the household. *Results*: The risk of lung cancer more than doubled for women who reported 40 or more smoke-years of household exposure during adulthood (odds ratio [OR] = 2.4; 95% confidence interval [CI] = 1.1-5.3) or 22 or more smoke-years of exposure during childhood and adolescence (OR = 2.4; 95% CI = 1.1-5.4). Risks were highest for non-adenocarcinoma lung cancers, although modest elevations in risk were also observed for adenocarcinomas. When a surrogate respondent other than the patient's husband provided information on exposure, the risk estimates were considerably lower. *Conclusion*: These findings suggest that long-term exposure to environmental tobacco smoke increases the risk of lung cancer in women who have never smoked. [J Natl Cancer Inst 84:1417–1422, 1992]

In 1986, reports by the Surgeon General (*1*) and the National Academy of Sciences (*2*) concluded that involuntary smoking can cause lung cancer in nonsmokers. More recently, the National Institute for Occupational Safety and Health released a bulletin that reached similar conclusions (*3*). Several additional studies have examined the relationship between environmental tobacco smoke and the development of lung cancer in nonsmokers. In 1991, Fontham et al. (*4*) reported the results of the first 3 years of a large multicentered study of lung cancer risk among female lifetime nonsmokers. For nonsmoking women living with a spouse who smoked, there was a 50% increase in risk for development of lung adenocarcinomas. In addition, there was a significant increase in risk for nonsmoking women exposed to environmental tobacco smoke at work or during social activities. No association was noted for nonsmoking women exposed to environmental tobacco smoke during childhood. In contrast, Janerich et al. (*5*) found that exposure to high levels of household smoke during childhood and adolescence doubled the risk of lung cancer among male and female nonsmokers, whereas exposure to smoke during adulthood was not associated with an excess risk. Other authors (*6-8*) noted an increase in lung cancer risk among the offspring of smokers, but their study populations included few children who were not cigarette smokers themselves.

The current study further explores the effect of environmental tobacco smoke and other risk factors for lung cancer on women who have never smoked tobacco.

Patients and Methods

A population-based case-control study was conducted in central Florida to examine the causes of lung cancer in nonsmoking women. Women were eligible for inclusion as case patients if they had a histologically confirmed primary

Received February 24, 1992; revised May 2, 1992; accepted June 5, 1992.

Supported by Public Health Service grant CA-45513-05 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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We thank all of the hospitals in the area who participated in the study and the Statewide Cancer Registry, Department of Health and Rehabilitative Services, Tallahassee, Fla. The authors assume full responsibility for the analyses and interpretation of the data.

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carcinoma of the lung (International Classification of Diseases for Oncology codes 162.2-162.9) that was diagnosed between April 1, 1987, and February 28, 1991, and if they resided at the time of diagnosis in a 28-county area in central Florida. These women were identified through the tumor registries of area hospitals and the Florida Cancer Data System of the Statewide Cancer Registry. Control subjects were community based and were identified through random-digit dialing. All case patients and control subjects were lifetime nonsmokers, defined as having smoked for a total of less than 6 months or having smoked less than 100 cigarettes in their lifetimes.

The smoking status of potential case patients in the study was confirmed at several stages. Once these individuals were identified by their hospital or the Statewide Cancer Registry records, their smoking status was confirmed when their physician was contacted for permission to interview, again at the time of initial contact with the patient or next of kin, and, finally, at the commencement of the interview. In addition, the interview contained questions regarding experimentation with tobacco, designed to elicit in a neutral manner any prior undisclosed tobacco use. Any potential case patient whose smoking status could not be confirmed was excluded. Of those found to be eligible, 83% of the case patients or their next of kin agreed to be interviewed. The smoking status of control subjects was determined during random-digit dialing and verified during the interview.

Trained interviewers interviewed case patients and control subjects either in person or over the telephone. When necessary, questionnaires were mailed. Of the case patient interviews, 41% were obtained by in-person contact, 51% by telephone, and 8% by mail. Of the control subject interviews, 53.8% were obtained by in-person contact, 45.9% by telephone, and 0.3% by mail. Informed consent was obtained from the case patients and control subjects prior to the interviews according to the guidelines of the University of South Florida Institutional Review Board. The interview included questions on environmental tobacco smoke exposures at home, on the job, and in social settings. If case patients were too ill to be interviewed or were deceased, surrogate respondents (primarily husbands and children) were interviewed. Interviews of surrogate respondents were necessary for 66.7% of the case patients.

Odds ratios (ORs) were calculated to estimate the relative risks. Multiple logistic regression analyses were performed using the SAS LOGISTIC procedure (SAS Institute, Cary, N.C.). Ninety-five percent confidence intervals (CIs) were calculated from the logistic models. The chi-square statistic was used to test for trend.

Results

The study population consisted of 210 women with histologically confirmed primary lung cancer who had never smoked (case patients) and 301 community-based control women who had never smoked (control subjects). The basic demographic characteristics of the case patients and control subjects are presented in Table 1. Ninety-three percent of the case patients and 94% of the control subjects were White. (The small percentage of non-White study participants reflects the small percentage [5%] of non-White case patients identified by hospitals and the statewide cancer registry.) Case patients tended to be somewhat older and had fewer years of formal education than controls, with a significant trend of increasing lung cancer risk with decreasing years of schooling ($P = .019$). Almost half of the case patients and control subjects had lived in Florida for at least 20 years.

Table 2 indicates the ORs and 95% CIs associated with exposure to cigarette smoke from parents, siblings, husbands, and other household members, after adjustment for age, race, and education. Unexposed individuals were those with no household environmental tobacco smoke exposure. We describe exposure in terms of smoke-years, defined as the sum of the reported years of exposure to cigarette smoke from each smoker in the household. We considered smoke-years to be a more reliable measure of exposure than pack-years, since study participants had less difficulty recalling the number of years they had lived with someone who smoked than recalling the number of cigarettes per day to which they had been exposed. Smoke-years were subdivided into three categories of approximately equal size

Table 1. Distribution of selected characteristics of case patients and control subjects

Characteristic	Case patients (n = 210)*		Control subjects (n = 301)*	
	No.	%	No.	%
Race				
White	196	93	284	94
Non-White	14	7	17	6
Birth year				
Before 1920	137	65	179	60
1920-1929	52	25	73	24
1930 or later	21	10	49	16
Marital status				
Married	108	51	174	58
Other	102	49	127	42
Years of education				
≤8 grades	38	18	37	12
9-11 grades	36	17	40	13
≥12 grades	135	65	223	74
Year in Florida				
<10	47	22	65	22
10-19	63	30	89	30
20-29	34	16	46	15
≥30	66	31	101	34
Lung cancer cell types				
Adenocarcinoma	129	61		
Squamous cell carcinoma	36	17		
Small-cell carcinoma	14	7		
All other	31	15		

*Values may not add to total because of missing data

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for both early and adult years. The distribution of smoke-years of exposure was much lower for early years, primarily because participants tended to live with spouses for more years than they had lived with their parents, resulting in lower cutoff points.

Lung cancer risk estimates for women who were exposed to environmental tobacco smoke during childhood and adolescence are shown in Table 2. When we calculated the risk associated with exposure to smoke from family members on an individual basis (mother, father, siblings, and others), there was a slight increase in risk for all exposures, although the increases in risk were not statistically significant. However, when we calculated risk according to smoke-years of exposure, which reflects total exposure to smoke from all household members, a significantly elevated risk of 2.4 (95% CI = 1.1-5.4) was observed for women exposed 22 years or more.

Table 2 also shows the effect of environmental tobacco smoke exposure during adulthood on lung cancer risk. Women who lived for 40 or more years of their adult lives with husbands and other individuals who smoked were found to have an elevated risk of 2.4 (95% CI = 1.1-5.3). If we considered only smoke exposure from husbands for 40 or more smoke-years (data not shown), the risk estimate decreased slightly to 2.2 (95% CI = 1.0-4.9).

In terms of total lifetime smoke-years of exposure (Table 2), no significant excess risks were observed for women reporting fewer than 40 lifetime smoke-years, but women reporting 40 or more years of exposure experienced an elevated lung cancer risk of 2.3 (95% CI = 1.1-4.6).

We also examined the relationship between the lung cancer risk associated with environmental tobacco smoke exposure and lung cancer cell type. Since 61.4% of the lung cancers in the study were adenocarcinomas, all lung cancer histologies other than adenocarcinoma were combined in one group for analysis. Risk estimates for smoke-years of exposure were calculated separately for the two groups, and the results are shown in Table 2.

For women with adenocarcinoma, the risks were slightly elevated for all categories of smoke exposure, but the results did not achieve statistical significance. Women with non-adenocarcinoma lung cancers, on the other hand, showed significantly elevated risks when their exposure to environmental tobacco smoke was of long duration. The OR indicated a threefold increased risk of lung cancer for women who reported 22 or more smoke-years of exposure from parents, siblings, and others during childhood and adolescence (OR = 3.4; 95% CI = 1.1-10.6). Similarly, women with 40 or more years of adulthood exposure to smoke from husbands and other household members experienced a significant elevation in risk (OR = 3.3; 95% CI = 1.1-9.8). When total lifetime exposure to environmental smoke was considered, the OR was 3.3 (95% CI = 1.2-8.9) for the highest exposure level. For women with non-adenocarcinoma lung cancers, there was a statistically significant trend of increasing risk associated with increasing smoke-years of exposure for each type of exposure (childhood, adulthood, and lifetime).

Since surrogate respondents were required for about two thirds of the case patient interviews, we investigated whether the source of the case patient interview (self-respondent versus surrogate respondent) affected the risk estimates. Surrogate respondents for case patients were divided into two groups, "husbands" and "other surrogates," the latter group consisting primarily of sons and daughters. The results of this analysis are shown in Table 3. Because the number of respondents in some categories was very small, analysis of risk associated with exposure to smoke from individual household members is limited to fathers and husbands. In comparison with the risk estimates for women whose interviews were completed by themselves or by their husbands, the risk estimates for women in the "other surrogate" respondent category were considerably lower. This result was true both for risk associated

Table 2. Effect of environmental tobacco smoke on lung cancer risk of nonsmoking women, according to tumor cell type

	All lung cancers			Adenocarcinomas			All other cell types		
Exposure history	OR*	95% CI	*P* for trend	OR*	95% CI	*P* for trend	OR*	95% CI	*P* for trend
Exposure: yes/no									
Mother	1.6	0.6-4.3		1.6	0.5-5.4		1.7	0.3-8.2	
Father	1.2	0.6-2.3		1.1	0.5-2.4		1.4	0.5-3.7	
Siblings and others	1.7	0.8-3.9		1.3	0.6-2.7		1.4	0.6-3.7	
Husbands	1.6	0.8-3.0		1.3	0.6-2.7		2.2	0.8-5.8	
Smoke-years									
Childhood/adolescence (parents and siblings)									
<18	1.6	0.7-3.6		1.8	0.7-4.4		1.3	0.4-4.3	
18-21	1.1	0.5-2.6		1.1	0.4-3.0		1.3	0.3-4.6	
≥22	2.4	1.1-5.4	.114	1.9	0.7-5.0	.491	3.4	1.1-10.6	.041
Adulthood (husbands and others)									
<22	1.6	0.8-3.2		1.7	0.8-3.7		1.5	0.5-4.2	
22-39	1.4	0.7-2.9		1.1	0.5-2.5		2.0	0.7-5.4	
≥40	2.4	1.1-5.3	.025	1.8	0.7-4.7	.320	3.3	1.1-9.8	.005
All lifetime household exposure									
<22	1.3	0.6-2.5		1.2	0.5-2.7		1.2	0.4-3.4	
22-39	1.4	0.7-2.9		1.2	0.5-2.7		1.5	0.6-4.2	
≥40	2.3	1.1-4.6	.004	1.7	0.8-3.9	.491	3.3	1.2-8.9	.001

*OR, adjusted for age, race, and education (≤8 and >8 grades)

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Table 3. Effect of environmental tobacco smoke on lung cancer risk of nonsmoking women, according to source of case patient interview

Exposure history	Source of case patient interview							
	Self (n = 70)		Husband (n = 48)		Other surrogate (n = 92)		Self and husband (n = 118)	
	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Exposure: yes/no								
Father	3.2	0.9-11.3	2.0	0.4-8.8	0.6	0.3-1.3	2.7	1.0-7.3
Husband	3.1	0.9-10.6	3.1	0.7-13.7	0.9	0.4-1.9	3.1	1.2-8.3
Siblings and others	—	—	—	—	—	—	4.3	1.3-14.2
Smoke-years								
Childhood/adolescence (parents and siblings)								
<18	4.3	1.1-16.7	2.4	0.4-12.8	0.6	0.2-1.9	3.6	1.2-10.8
18-21	2.4	0.5-10.6	1.6	0.2-10.5	0.6	0.2-2.0	2.1	0.6-7.2
≥22	6.5	1.7-25.5	1.4	0.2-9.6	1.6	0.5-4.8	4.4	1.4-13.5
P for trend		.04		.78		.68		.07
Adulthood (husband and others)								
<22	3.4	0.9-12.2	3.1	0.7-14.8	0.8	0.3-2.0	3.3	1.2-9.2
22-39	3.6	1.0-13.1	1.8	0.4-9.2	0.8	0.3-1.9	2.9	1.0-8.2
≥40	4.7	1.2-19.1	4.2	0.8-22.9	1.5	0.6-3.9	4.7	1.5-14.7
P for trend		.02		.05		.35		.006
All lifetime household exposure								
<22	2.0	0.5-7.6	3.2	0.7-14.9	0.6	0.3-1.6	2.5	0.9-7.2
22-39	4.4	1.3-15.6	1.0	0.2-5.6	0.6	0.2-1.4	3.1	1.1-8.6
≥40	4.1	1.1-14.8	3.5	0.7-16.7	1.5	0.7-3.6	4.0	1.4-11.3
P for trend		.01		.15		.11		.004

*OR, adjusted for age, race, and education (≤8 and >8 grades).

with exposure to smoke from individual household members and for risk associated with household smoke-years of exposure.

Given that the risk estimates for self-respondents and spouse respondents were so similar, we repeated the analysis, excluding "other surrogate" respondents. As shown in Table 3, limiting the case patients to self-respondents and spouse respondents resulted in significantly elevated risks associated with exposure during childhood and adolescence to smoke from siblings and others (OR = 4.3; 95% CI = 1.3-14.2) and with exposure during adulthood to smoke from husbands (OR = 3.1; 95% CI = 1.2-8.3). When smoke-years of exposure were considered, statistically significant increases in risk were seen for the lowest and highest categories of smoke-years of exposure to smoke from parents and siblings; the risk estimate for the highest exposure category was elevated to 4.4 (95% CI = 1.4-13.5). When smoke-years of adulthood exposure to smoke from husbands and others were considered, statistically significant elevations in risk were seen for the lowest and highest exposure categories and borderline significance was found for the intermediate category. For the highest exposure category, the risk estimate increased to 4.7 (95% CI = 1.5-14.7). When lifetime household exposure was considered, a clear dose-response effect was evident: Risk estimates increased from 2.5 for fewer than 22 smoke-years of exposure to 4.0 for 40 or more years of exposure. The sample became small when we considered differences between lung cancer cell types for the different respondent groups; nevertheless, higher estimates were still associated with women diagnosed with non-adenocarcinoma lung cancers, consistent with the analysis from the full data set.

We found no statistically significant increase in risk associated with exposure to environmental tobacco smoke at work or during social activities (data not shown).

Discussion

The results of our study indicate that the risk of lung cancer is increased among women who are themselves lifetime nonsmokers but who live in households with smokers. Elevated risks were seen most consistently when exposures to household smoke occurred during adulthood. Women with non-adenocarcinoma lung cancers who reported high levels of exposure to household smoke had the most pronounced elevation in risk. There was suggestive evidence that prolonged exposure to tobacco smoke during childhood and adolescence might also be associated with an increased risk of lung cancer.

An association between exposure to environmental tobacco smoke and the development of non-adenocarcinoma lung cancers has been noted in several other investigations, both in the United States and abroad. In a study that pooled data from three case-control studies in the United States, Dalager et al. (*9*) reported an almost threefold increased risk of squamous cell and small-cell lung carcinomas among male and female lifetime nonsmokers who were married to smokers, but they observed no increased risk of adenocarcinomas. Garfinkel et al. (*10*) investigated the distribution of various lung cancer histologies among lifetime nonsmoking women in New Jersey and Ohio. They found that women whose husbands smoked had a fivefold increase in risk of squamous cell lung carcinomas, but no statistically significant increase in risk of other types of lung cancer. In a study conducted in Louisiana, Correa et al. (*6*) reported a doubling of lung cancer risk among nonsmokers married to smokers, both male and female. Although the risk estimates were not presented according to histologic classification of the lung cancers, the authors

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indicated that the exclusion of adenocarcinomas from their analysis produced a statistically significant linear trend of increasing risk with increasing exposure.

In an investigation of non-adenocarcinoma lung cancers in nonsmoking Athenian women, Trichopoulos et al. (*11*) reported a risk estimate of 2.4 for women whose husbands smoked fewer than 21 cigarettes per day and a risk estimate of 3.4 for women whose husbands smoked more than 20 cigarettes per day. An association between marriage to a smoker and an increased risk of small-cell and squamous cell lung carcinomas was also observed in a study of Swedish women (*12*). For other lung cancer cell types in the Swedish study, the risks were close to unity except in the case of women with high exposure levels, whose risk was doubled. A study of lifetime nonsmoking women in Hong Kong by Koo et al. (*13*) showed that exposure to environmental tobacco smoke was associated with an elevated risk of squamous cell and large-cell carcinomas. These results conflict with those observed in a multicentered study in the United States (*4*), where an elevated risk of lung cancer attributable to passive smoking was limited to patients with adenocarcinoma; these individuals experienced an almost 50% increase in risk. In another study conducted in Hong Kong, Lam et al. (*14*) reported that lifetime nonsmoking women with husbands who smoked had an increased risk for the development of small-cell carcinomas, adenocarcinomas, and large-cell carcinomas, but not squamous cell carcinomas.

Our analysis of the effect of cigarette smoke exposure during childhood and adolescence on lung cancer risk revealed an increased risk in women with 22 or more total smoke-years of exposure. This excess risk for the highest exposure category was statistically significant for all lung cancers combined and for non-adenocarcinoma lung cancers. A positive association between lung cancer risk and high levels of environmental smoke exposure at a young age has also been reported by Janerich et al. (*5*), and an increased overall cancer risk among individuals exposed to cigarette smoke in childhood has been noted by Sandler et al. (*7*). In studies conducted by Correa et al. (*6*) and Wu et al. (*8*), the increased lung cancer risk resulting from childhood exposures was found to be associated specifically with maternal smoking, whereas in our study we observed less variation in risk according to which family member smoked.

In the interpretation of the results of this study, one area of particular concern is the impact of respondent type on the risk estimates. Although the risk estimates based on responses by the case patient and her husband are reasonably similar, given the sample size, the risk estimates based on "other surrogate" respondents (primarily sons and daughters) are considerably lower. One possible explanation is that the children of the case patients selectively underestimated the exposures that their mothers received, particularly from their fathers' cigarette smoke. Conversely, the case patients and their husbands may have overestimated the exposure. Few studies have presented risk estimates according to respondent type. Janerich et al. (*5*) observed that interviews with surrogate respondents produced lower passive smoking risk estimates than direct interviews. Data on variations within the surrogate group were not available. In another study on passive smoking, Garfinkel et al. (*10*) reported that the highest lung cancer risk estimates were based on responses by the children of the study subjects, a finding opposite to that reported here.

Another issue that must be considered in the evaluation of our findings is the possibility of misclassification of smokers as nonsmokers. Although every attempt was made to verify that the case patients were truly lifetime nonsmokers, only oral reports of smoking status were available. Fontham et al. (*4*) ascertained urinary cotinine levels to confirm self-reports of smoking status. The results of this validation procedure suggested that, depending on the urinary cotinine level selected to indicate active smoking, either 0.8% or 2.4% of case patients and 2% or 3.9% of population control subjects could have been misclassified as lifetime nonsmokers. If these same percentages are applied to our study, then two to five case patients and six to 12 control subjects may have been incorrectly classified as nonsmokers.

In any analysis that distinguishes between lung cancer cell types, the accuracy of the histological classification must be considered. In the present study, which included many hospitals throughout central Florida, an independent pathological review was not possible. However, the distribution of lung cancer cell types in our study was similar to that described by Fontham et al. (*4*), who did conduct an independent pathological review. In the latter study, the pathological review resulted in reclassification of approximately 25% of squamous cell carcinomas and 39% of large-cell carcinomas as adenocarcinomas. Of tumors originally classified as adenocarcinomas, 97% were correctly classified according to the independent reviewers. By extrapolation, any misclassifications in our own study would tend to reduce the differences in risk estimates between various lung cancer cell types, since the excess risks were associated primarily with non-adenocarcinomas.

In conclusion, the results described here suggest that long-term exposure to environmental tobacco smoke increases the risk of lung cancer in women who are nonsmokers. Risks appeared most elevated for non-adenocarcinoma lung cancers. High levels of exposure during youth and adulthood may each play a role in increasing lung cancer risk.

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Second Cancers in Patients With Chronic Lymphocytic Leukemia

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Background: **Reports to date have provided widely divergent estimates of the risk of second malignant neoplasms in patients with chronic lymphocytic leukemia (CLL), ranging from cancer deficits to excesses of twofold to threefold.** ***Purpose:*** **Our purpose was to estimate the risk of second primary cancers following CLL, utilizing population-based tumor registries, and to determine whether site-specific excesses might be associated with type of initial treatment for CLL.** ***Methods:*** **We analyzed data for 9456 patients diagnosed with CLL as a first primary cancer between 1973 and 1988, who were reported to one of nine tumor registries participating in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program and who survived 2 or more months. SEER files were searched for invasive primary malignancies that developed at least 2 months after the initial CLL diagnosis.** ***Results:*** **Compared with the general population, CLL patients demonstrated a significantly increased risk of developing all second cancers (840 observed; observed-to-expected ratio [O/E] = 1.28; 95% confidence interval [CI] = 1.19-1.37). Significant excesses were noted for cancers of the lung (O/E = 1.90), brain (O/E = 1.98), and eye (intraocular melanoma) (O/E = 3.97) as well as malignant melanoma (O/E = 2.79) and Hodgkin's disease (O/E = 7.69). Cancer risk, which did not vary according to initial treatment category, was also constant across all time intervals after CLL diagnosis.** ***Conclusion:*** **CLL patients are at a significantly increased risk of developing a second malignant neoplasm. The pattern of cancer excesses suggests a susceptibility state permitting the development of selected second malignancies in patients with CLL, perhaps because of shared etiologic factors, immunologic impairment, and/or other influences. Although our results do not suggest a strong treatment effect, more detailed studies of second tumors in CLL are needed to investigate the role of radiation therapy and chemotherapy. [J Natl Cancer Inst 84:1422–1427, 1992]**

Patients with chronic lymphocytic leukemia (CLL) exhibit a variety of immunologic perturbations (*1-4*) that may increase their risk for second malignant neoplasms. The occurrence of familial CLL may also suggest, for some subjects, genetic determinants (*5-7*), such as those that underlie other sets of multiple primary cancers (*8,9*). Moreover, radiotherapy and chemotherapeutic agents may also contribute to subsequent malignancies among cancer survivors (*10*). It is important to clarify the risk of second cancers in CLL patients because of the potential impact on patient management, follow-up, and survival. However, various reports to date have provided divergent estimates of the occurrence of second malignancies in CLL patients, ranging from cancer deficits to excesses of twofold to threefold (*11-20*). To further explore and quantify the risk of second cancers among a large number of CLL patients in the general population and to examine associations of risk with initial therapy, we conducted a survey of more than 9000 such subjects reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program[1] from 1973 through 1988. Since CLL patients are frequently treated only with alkylating agents without the confounding effects of radiotherapy, this group of patients provides a special opportunity to study the late sequelae of these drugs.

Patients and Methods

We analyzed all patients diagnosed with CLL as a first primary cancer between 1973 and 1988 who were reported to one of nine population-based cancer registries of the SEER Program and survived 2 or more months. Such registries include those in the metropolitan areas of

Received January 10, 1992; revised May 14, 1992; accepted June 4, 1992.

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We are indebted to the State Health Registry of Iowa (Ms. Kathleen McKeen and Dr. Charles F. Lynch) for data retrieval, to Drs. John Boice, Neil Caporaso, and Martha Linet for critical review of the manuscript, and to Ms. Sandy Coopersmith and Ms. Shirley Carson for secretarial support.

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[1]Ed. note: The program is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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FONTHAM, E.T.H., CORREA, P., WU-WILLIAMS, A., REYNOLDS, P., GREENBERG, R.S., BUFFLER, P.A., CHEN, V.W., BOYD, P., ALTERMAN, T., AUSTIN, D.F., LIFF, J., AND GREENBERG, S.D., "LUNG CANCER IN NONSMOKING WOMEN: A MULTICENTER CASE-CONTROL STUDY," CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 1: 35-43, 1992

This paper reports on an on-going multicenter case-control study. Nonsmoking female cases were defined as having never used any tobacco product. The study included 420 cases, 351 colon cancer controls, and 780 population controls. According to the authors, the study was "designed to minimize some of the methodological problems which have been of concern in previous studies of environmental tobacco smoke and lung cancer." The use of two control groups was intended to help in evaluating recall bias. In addition, histopathological review was conducted to confirm lung cancer cases and cell types; however, only 85% of the cases had complete histology. Finally, urinary cotinine was measured to investigate current tobacco use; however, cotinine analysis was completed for only slightly more than half of the cases. The authors suggested that their data "provide additional evidence in favor of a causal relationship between exposure to ETS and lung cancer in women who have never used tobacco themselves."

- Based on the index of ever having been exposed to spousal smoking during adulthood, an OR of 1.21 (95% CI 0.96-1.54) was presented. The numbers of cases and controls used in this analyses were not provided. Elsewhere, based on 264 cases, two spousal smoking risk estimates, neither statistically significant, were presented. They were 1.17 (95% CI 0.87-1.59) for colon cancer controls and 1.20 (95% CI 0.93-1.55) for population controls.

- The authors presented ORs for exposure during childhood to smoking by father or mother. None of the risk estimates was statistically significant. For father having smoked, the ORs were 0.91 (95% CI 0.67-1.24) for colon cancer controls and 0.82 (95% CI 0.64-1.07) for population controls, based on 196 cases. For mother ever having smoked, the ORs were 0.85 (95% CI 0.53-1.38) for colon cancer controls and 0.84 (95% CI 0.56-1.26) for population controls, based on 44 cases.

- The authors reported a statistically significant odds ratio of 1.34 (95% CI 1.03-1.73) for having reported occupational exposure to ETS. The numbers of cases and controls were not provided.

- A large number of subgroup analyses were conducted in this study; more than 65 ORs were presented.

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The authors reported elevated ORs for adenocarcinoma, such as statistically significant ORs ranging from 1.38 to 1.60 for exposure during adulthood to spousal smoking, smoking by other household members, occupational exposure, and social exposure. However, these data are not consistent with the data of Stockwell, et al., for instance, who reported higher ORs for other cell types when compared to adenocarcinoma.

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Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study[1]

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Abstract

The association between exposure to environmental tobacco smoke and lung cancer in female lifetime nonsmokers was evaluated using data collected during the first 3 years of an ongoing case-control study. This large, multicenter, population-based study was designed to minimize some of the methodological problems which have been of concern in previous studies of environmental tobacco smoke and lung cancer. Both a cancer control group and a population control group were selected in order to evaluate recall bias. A uniform histopathological review of diagnostic material was conducted for case confirmation and detailed classification. Biochemical determination of current exposure to tobacco and screening of multiple sources of information to determine lifetime nonuse were utilized to minimize misclassification of smokers as nonsmokers.

A 30% increased risk of lung cancer was associated with exposure to environmental tobacco smoke from a spouse, and a 50% increase was observed for adenocarcinoma of the lung. A statistically significant positive trend in risk was observed as pack-years of exposure from a spouse increased, reaching a relative risk of 1.7 for pulmonary adenocarcinoma with exposures of 80 or more pack-years. The predominant cell type of the reviewed, eligible lung cancer cases was adenocarcinoma (78%). Results were very similar when cases were compared to each control group and when separate analyses were conducted for surrogate and personal respondents. Other adult-life exposures in household, occupational, and social settings were each associated with a 40–60% increased risk of adenocarcinoma of the lung. No association was found between risk of any type of lung cancer and childhood exposures from a father, mother, or other household members.

Introduction

Approximately one decade has passed since the initial reports of increased risk of lung cancer in nonsmoking women married to smokers (1, 2). The ensuing studies have provided a body of data which suggests a small but significant elevation in risk of lung cancer associated with exposure to ETS[3] (3–22). In reported prospective studies exposure has been assessed by the spouse's smoking history, primarily that of husbands. In case-control studies, the primary ETS exposure assessed has also been that from a spouse, although exposures from parents, other household exposures, and the workplace have been examined in some studies.

In general, these studies have included fewer than 100 nonsmoking lung cancer cases whose self-reported smoking status has not been validated by biochemical determination or other means. Reviews of available studies of ETS and lung cancer in nonsmokers by the National Research Council (23), the International Agency for Cancer Research (24), and others (25, 26) have concluded that although misclassification is unlikely to account for all of the observed increased risk, some misclassification of current or former smokers as nonsmokers is likely (0.5–5.0%). Because smokers tend to marry smokers, misreporting may introduce some bias in the estimation of the magnitude of the observed effect.

This study was undertaken in 1985 in an effort to address a number of unresolved issues related to ETS:

(a) Misclassification of Smoking Status. Multiple sources of information are utilized to ascertain nonsmoking status (medical record, physician, and then the study subject or surrogate). Study respondents are questioned twice (at contact to set up the interview and at the beginning of the interview). Self-reported current nonsmoking status is corroborated by measurement of urinary cotinine.

(b) Histopathological Specificity. Microscopic diagnostic slides are reviewed by one pulmonary pathologist both to confirm eligibility of cases as primary lung carcinomas and to provide a detailed review (subtype, differ-

Received 5/2/91.
[1] This research was supported by Grant CA40095 from the National Cancer Institute.
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[3] The abbreviations used are: ETS, environmental tobacco smoke; SEER, Surveillance, Epidemiology, and End Result; OR, odds ratio; CI, confidence interval.

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entiation) and classification of the histopathological cell type.

(c) Recall Bias. Two control groups, one with colon cancer and one from the general population, are selected for case-control comparisons. Differential recall between cases and colon cancer controls should be minimized since both groups are similarly motivated to recall earlier exposures.

(d) Source of ETS Exposure. Information on childhood exposures from a father, mother, and other household members and adult exposures from husband(s), other household members, and occupational and social settings is obtained by questionnaire. The risk associated with exposure to ETS from different sources and during different time periods can be evaluated.

(e) Confounders and Other Risk Factors. Because the magnitude of the main ETS effect is expected to be small, it is important to take into account potential confounding factors and effect modifying factors in a study with a sufficiently large number of cases and controls. It is anticipated that upon completion of this study about 600 cases and twice that number of controls will have participated.

This report represents findings from the ongoing study and includes the largest number of lifetime nonsmokers with lung cancers reported to date. This report was felt to be justified given the public health importance of the issue under investigation.

Methods

The study is a population-based case-control study of lung cancer in women who have never used any tobacco product. This preliminary report includes cases diagnosed during the first three years (December 1, 1985 through December 31, 1988) of a 5-year study. At the time of diagnosis cases were residents of one of five major metropolitan areas throughout the United States, including Atlanta (Clayton, Cobb, DeKalb, Fulton, and Gwinnett counties), Houston (Galveston and Harris counties), Los Angeles (Los Angeles County), New Orleans (Jefferson, Orleans, and St. Bernard parishes), and the San Francisco Bay Area (Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara counties), representing a population of approximately 18.5 million people or 8% of the U. S. population.

Case and Control Selection

Rapid case ascertainment procedures, which included review of pathology reports from study hospitals, were utilized to identify potentially eligible lung cancer cases. Eligible cases included English-, Spanish-, or Chinese-speaking females, aged 20-79, who had a histopathologically confirmed diagnosis of primary carcinoma of the lung (International Classification of Disease, 9th Revision, code 162) made prior to death, had no history of previous cancer, and who were lifetime nonusers of tobacco. Lifetime nonusers of tobacco are defined for this study as persons who had smoked fewer than 100 cigarettes and had not used any other form of tobacco for more than 6 months.

Two control groups were selected. The first control group, referred to as the population control group, was selected by random digit dialing and supplemented by random sampling from the files of the Health Care Financing Administration for women aged 65 and older. Controls were frequency matched to cases on age (<50, 50-59, 60-69, 70+ years) in a 2:1 control:case ratio. They met the same eligibility criteria as cases for age, residence, language, and tobacco use.

Females, aged 20-79, with a diagnosis of primary carcinoma of the colon (International Classification of Disease, 9th Revision, code 153) who met the language, previous cancer, lifetime nonsmoking, and residential eligibility criteria of the cases, were identified and frequency matched to lung cancer cases by 10-year age groups and race. This second control group was selected because there is no established increased risk of colon cancer associated with either active or passive smoking, and it provided an opportunity to examine the issue of recall bias associated with a recent diagnosis of cancer.

A multistep procedure was used to determine lifetime smoking status. After identification of a potentially eligible lung cancer case or colon cancer control, the hospital chart was reviewed to obtain demographic data and available information on tobacco use. Patients identified as current or former smokers in the medical record were considered ineligible. In study areas where individual physician notification was required/preferred, the tobacco use history was requested from the physician for potentially eligible cases and colon controls identified as nonusers of tobacco or with unknown smoking status according to the hospital record. Women who were identified as current or former smokers by their physicians were considered ineligible. All remaining cases and colon cancer controls believed to be nonsmokers or with unknown smoking status were contacted by telephone to elicit information on tobacco use. Women who reported ever smoking 100 or more cigarettes or using any other form of tobacco for more than 6 months were considered ineligible. The identical telephone screening procedure was used for the population control group. At the time of the interview, the tobacco use screening questions were repeated to confirm each study subject's reported nonuse of tobacco.

The questionnaire was translated from English into Spanish and Chinese, and interviewers fluent in those languages conducted the non-English as well as English interviews. Interviews were completed for 431 of 514 incident cases (84%), 358 of 489 colon cancer controls (73%), and 794 of 1105 population controls (72%). Sixty-one (3.8%) of the interviews were conducted in Spanish ($n = 14$) or Chinese ($n = 47$): 22 cases (5%); 23 colon cancer controls (6%); and 16 population controls (1.5%). A next-of-kin interview was solicited for lung cancer cases and colon cancer controls who were too ill or deceased. All population controls were self-respondents because of the sampling method used to identify these controls. A total of 143 lung cancer case interviews and 35 of 352 colon cancer control interviews were conducted with next-of-kin respondents, representing 34% and 10% of the eligible respondents.

An extensive structured questionnaire obtained information concerning household, occupational, and other exposures to environmental tobacco smoke during the study subject's lifetime. Data were also collected on lifetime occupational history, usual adult diet, family and personal medical histories, and other exposures of interest, which are not included in this report.

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Table 1 Urinary cotinine/creatinine (ng/mg) by case-control status

	Lung cancer cases	Colon cancer controls	Population controls
Status			
Completed	239	260	684
Eligible (<100 ng/mg)	237	253	670
Ineligible (≥100 ng/mg)	2	7	14
Not performed			
Self-respondents	58	66	110
Next-of-kin respondents	134	32	
Results			
Eligible (<100 ng/mg)			
Mean (SD)	6.95 (12.11)	5.82 (11.68)	9.68 (12.88)
Median	2.0	0	5.4
Range	0-71.4	0-88.4	0-95.01
Ineligible (≥100 ng/mg)			
Range	131-219	145-5,163	103-14,014

Table 2 Pathology review

Reviewed, found to be eligible	359 (85%)
Adenocarcinoma	281
Large cell carcinoma	43
Squamous cell carcinoma	20
Small cell carcinoma	12
Others and not otherwise specified	3
Not reviewed/insufficient material	50 (12%)
Histology by hospital pathologist	
Adenocarcinoma	30
Large cell carcinoma	5
Squamous cell carcinoma	7
Small cell carcinoma	2
Others and not otherwise specified	6
Review pending	11 (3%)
Total cases	420
Reviewed, found to be ineligible	9

Eligibility Review Procedures

Biochemical Determination of Current Tobacco Use. Cotinine, a major metabolite of nicotine, is an indicator of recent exposure to tobacco (27). Urinary cotinine was used to corroborate self-reported current nonsmoking status of study subjects. A urine sample was collected from all consenting study subjects at the time of interview. The specimens were stored at −20°C until shipment to the American Health Foundation for analysis.

Cotinine was quantitated by radioimmunoassay using the method of Haley *et al.* (28) with a modification of the antibody of Langone *et al.* (29). Cotinine levels were adjusted for urine flow based on creatinine values by determining the cotinine/creatinine ratio. Creatinine was determined by spectrophotometry using the Kodak Ektachem 400 Clinical Chemistry Analyzer.

At this time biochemical analysis is complete for 239 of 431 cases (55.5%), 260 of 358 colon cancer controls (72.6%), and 684 of 794 population controls (86.1%) (Table 1). Two of 239 case samples (0.8%), 7 of 260 colon cancer control samples (2.6%), and 14 of 684 population control samples (2.0%) had cotinine/creatinine levels of 100 ng/mg or greater. There is no established cotinine/creatinine level which clearly discriminates smokers from true nonsmokers heavily exposed to ETS. Under relatively high levels of exposure to ETS in aircraft and in exposure chambers, urinary excretion has reached a level of 55 ng/mg creatinine (30, 31). In this study, women whose cotinine/creatinine level exceeded 100 ng/mg were excluded from the study to eliminate persons likely to be active smokers, while allowing for the possibility of very high ETS exposures reflected in urinary levels of 56-99 ng/mg creatinine. Had the lower value of 55 ng/mg been selected as a cutpoint to avoid possible misclassification of active smokers as nonsmokers, 4 additional cases (1.6%), 2 colon cancer controls (0.8%), and 13 population controls (1.9%) would have been excluded from the analyses, with negligible effect on the results.

Histopathological Review. Representative diagnostic microscopic tissue slides for each case were requested from the hospital. These slides were reviewed by one pathologist specializing in pulmonary pathology. A total of 368 of 429 (86%) potential cases have undergone review. As shown in Table 2, 359 (98%) of the reviewed cases were confirmed as primary bronchogenic carcinoma. The histopathological primary cell type of the eligible cases is as follows: adenocarcinoma, 78%; large cell carcinoma, 12%; squamous cell carcinoma, 6%; small cell carcinoma, 3%; others, 1%. The histopathological cell type distributions were similar in the five study centers.

The overall concordance between the review pathology diagnosis and the original hospital pathology diagnosis was 81% (Table 3). The concordance varied greatly by histopathological cell type. Ninety-seven % (237 of 244) of the cases originally classified as adenocarcinomas were confirmed as this histopathological type upon review. Similarly, 10 of 11 (91%) of small cell carcinomas were so classified upon review. Concordance rates of 56% and 67% were seen for large cell and squamous cell carcinomas, respectively. A relatively large proportion of cases originally classified as large cell or squamous cell carcinomas were classified as adenocarcinomas by the review pathologist: 18 of 46 (39%) and 6 of 24 (25%), respectively. Based on hospital pathology reports, 34 subjects were categorized as "other primary lung carcinomas" which primarily included diagnoses of poorly differentiated carcinoma, bronchogenic carcinoma not otherwise specified, or malignant cells not otherwise specified. Upon review, 94% of these cases were classified into more specific histopathological cell types.

The nine cases (2%) found not to have primary bronchogenic carcinoma on review were excluded from all analyses. Three of these nine cases were determined to be carcinoid tumors, two were lymphomas, three were carcinomas metastatic to the lungs from other primary sites, and one was a benign neoplasm. The 61 cases that have not undergone histopathological review are included in analyses of all lung cancers combined (n = 420) but are not included in analyses stratified by histopathological type.

Statistical Analyses

Exposure to ETS was examined by source. Sources include both adult and childhood exposures as follows: spouse, other household members; occupational ETS exposures; and social or leisure time (nonhousehold, nonoccupational) ETS during adult life; and father, mother, and other household members who lived in the

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Table 3 Distribution of lung cancer histopathological cell types by hospital diagnosis and review diagnosis

Review diagnosis	Hospital diagnosis					
	Adenocarcinoma	Large cell carcinoma	Squamous cell carcinoma	Small cell carcinoma	Other lung carcinoma	Total
Adenocarcinoma	237	18	6	1	19	281
Large cell carcinoma	6	26	1	0	10	43
Squamous cell carcinoma	0	2	16	0	2	20
Small cell carcinoma	0	0	1	10	1	12
Other primary lung carcinomas	1	0	0	0	2	3
Total	244	46	24	11	34	359

home 6 months or more during childhood. Childhood was defined as the first 18 years of life. Exposures from parents after that time were classified as other household members during adult life. Dichotomous ETS exposures were first examined (ever or never) by type of tobacco: cigarettes; pipe; cigar; or any of these types of tobacco. Dose was estimated, as appropriate, by intensity (*e.g.*, number of cigarettes/day), duration (*e.g.*, number of years exposed), or a combination (e.g., pack-years). Pack-years of cigarette exposure from the spouse were calculated by multiplying the number of packs smoked per day by the number of years the spouse smoked cigarettes while living with the study subject. Pack-years of exposure were summed for all smoking spouses of each study subject.

One of the objectives of this study was to evaluate the association of ETS with specific histopathological cell types of lung cancer. The skewed distribution of histopathological types precluded any meaningful analysis by specific cell type other than adenocarcinoma and all other cell types combined. The results are presented for all lung cancers combined ($n = 420$) and adenocarcinomas confirmed by histopathological review ($n = 281$).

Cases were compared to each control group with regard to the distribution of relevant covariates such as age, education, income, and race/ethnicity. The association of ETS exposure with lung cancer risk was investigated first in contingency tables stratified by design or sampling variables (age, race, study center) and relevant covariates. Summary adjusted odds ratios and test statistics were calculated by the method of Mantel and Haenszel (32). Unconditional logistic regression analyses were then used to estimate the associations by summary adjusted odds ratios, confidence limits, and test statistics (33, 34).

Results

Demographic characteristics of cases and controls are presented in Table 4. Cases and controls were similar with respect to matching variables and most demographic variables. The largest number of cases ($n = 160$, 38%) were residents of Los Angeles, followed by cases from the San Francisco Bay Area ($n = 149$, 35%), and then the three smaller study centers in the southern United States: Atlanta ($n = 46$, 11%); Houston ($n = 39$, 9%); and New Orleans ($n = 26$, 6%).

The age distribution of cases and controls is uniform, with 73 to 74% of each series between the ages of 60 through 79. The proportion of older women in this group of female nonsmokers with lung cancer is higher than that among all female lung cancer cases in the SEER Program 1974–1986, in which only 48% of the cases were aged 65 or older (35).

Cases tended to have a somewhat lower household income and less education than the population controls. Approximately 35% of cases and controls spent their childhood in cities with populations of 50,000 or more, and the majority of cases and controls (70%, 68%, 77% for cases, colon cancer controls, and population controls, respectively) resided in cities during most of their adult life.

The estimated risks of lung cancer in nonsmoking women associated with ever having lived with a spouse who smoked are presented in Table 5. The adjusted ORs and the 95% CI are very similar for all spouse-related exposures regardless of control group. For all histopathological types of lung cancer combined, a 30% increase in risk is observed (OR = 1.28 and 1.29 with colon cancer and population controls). For each of the three types of tobacco smoked, the ORs ranged from 1.14 to 1.26. When the case series is restricted to the 281 pulmonary adenocarcinomas confirmed by histopathological review, the association is more pronounced. Approximately 50% elevations in risk of adenocarcinomas of the lung ($P < 0.05$) are associated with any use of tobacco by spouse(s), and cigarette smoking accounts for most of the tobacco use. The estimated relative risk of pulmonary adenocarcinoma associated with cigarette smoking by spouses was 1.36 (1.02–1.84) with the population controls as comparison and 1.31 (0.94–1.84) with the colon cancer controls as comparison. No association between spouses' tobacco use and lung cancers other than adenocarcinoma (squamous cell, small cell, large cell, and other; $n = 78$) was observed.

Separate analyses were conducted for subjects who personally responded and for whom information was obtained from surrogate respondents. The odds ratios for involuntary exposure to ETS were very similar for both groups of respondents; therefore, the results are not presented in the tables separately by type of respondent. One such example is the estimated relative risk of pulmonary adenocarcinomas associated with cigarette smoking by the spouse: OR = 1.38 and 1.30 for surrogate and self-respondents, respectively, comparing cases to colon cancer controls.

Effects by study center were also examined. The odds ratios by center ranged from a low of 1.17 to a high of 2.64 for risk of pulmonary adenocarcinoma associated with spouses' cigarette smoking. Because of the limited sample sizes, none of the individual study center esti-

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Table 4 Distribution of lung cancer cases and controls according to selected demographic characteristics

	Lung cancer cases (n = 240)		Colon cancer controls (n = 351)		Population controls (n = 780)	
	No.	(%)	No.	(%)	No.	(%)
Study center						
Atlanta	46	(11.0)	44	(12.5)	76	(9.7)
Houston	39	(9.3)	35	(10.0)	24	(3.1)
Los Angeles	160	(38.1)	125	(35.6)	358	(45.9)
New Orleans	26	(6.2)	18	(5.1)	44	(5.6)
San Francisco Bay Area	149	(35.5)	129	(36.7)	278	(35.6)
Respondent						
Study subject	277	(66.0)	316	(90.1)	780	(100.0)
Next of kin	143	(34.0)	35	(9.9)		
Age (years)						
20-29	5	(1.2)	1	(0.3)	9	(1.2)
30-39	11	(2.6)	13	(3.7)	42	(5.4)
40-49	23	(5.5)	22	(6.3)	30	(3.9)
50-59	73	(17.3)	55	(15.6)	121	(15.5)
60-69	147	(35.0)	105	(29.8)	221	(28.3)
70-79	161	(38.3)	155	(44.0)	357	(45.8)
Race/ethnic group						
White	266	(63.3)	240	(68.5)	503	(64.5)
Black	44	(10.5)	59	(16.8)	107	(13.7)
Hispanic	32	(7.6)	14	(4.0)	42	(5.4)
Asian	67	(16.0)	35	(10.0)	113	(14.5)
Other	11	(2.6)	2	(0.6)	13	(1.7)
Unknown/refused to answer	0	(0.0)	1	(0.2)	2	(0.4)
Annual income						
<$8,000	72	(17.1)	60	(17.1)	98	(12.6)
$8,000-12,999	63	(15.0)	52	(14.8)	115	(14.7)
$13,000-19,999	48	(11.4)	48	(13.7)	110	(14.1)
$20,000-34,999	73	(17.4)	61	(17.4)	153	(19.6)
$35,000-49,999	37	(8.8)	49	(14.0)	82	(10.5)
≥$50,000	59	(14.1)	35	(10.0)	128	(16.4)
Unknown/refused to answer	68	(16.2)	46	(13.1)	94	(12.0)
Education						
Less than high school	135	(32.1)	84	(23.9)	165	(21.2)
High school	140	(33.3)	134	(38.2)	246	(31.5)
Some college	71	(16.9)	74	(21.1)	181	(23.2)
College	33	(7.9)	28	(8.0)	107	(13.7)
Graduate	25	(6.0)	22	(6.3)	69	(8.9)
Unknown	16	(3.8)	9	(2.6)	12	(1.5)
Usual childhood residence						
Farm	93	(22.1)	78	(22.2)	131	(16.8)
Rural area	49	(11.7)	36	(10.3)	61	(7.8)
<20,000 population	92	(21.9)	81	(23.1)	196	(25.1)
20,000-49,999 population	37	(8.8)	46	(13.1)	98	(12.6)
≥50,000 population	146	(34.8)	109	(31.1)	291	(37.3)
Unknown	3	(0.7)	1	(0.3)	3	(0.4)
Usual adult residence						
Farm	23	(5.5)	15	(4.3)	10	(1.3)
Rural area	10	(2.4)	6	(1.7)	13	(1.7)
<20,000 population	39	(9.3)	28	(8.0)	45	(5.8)
20,000-49,999 population	53	(12.6)	61	(17.4)	108	(13.9)
≥50,000 population	293	(69.8)	240	(68.4)	601	(77.0)
Unknown	2	(0.5)	1	(0.3)	3	(0.4)

mates were statistically significant, and they did not significantly differ from one another.

Estimates of relative risk associated with the number of cigarettes smoked by a spouse were significantly elevated only in the highest exposure category, 40 or more cigarettes/day: 2.06 (1.19-3.54) and 1.69 (1.28-2.61) for adenocarcinoma of the lung comparing cases to colon cancer and population controls, respectively. Odds ratios were similar, although slightly lower, for all types of lung cancer combined: 1.70 (1.02-2.84) and 1.36 (0.90-2.06).

Pack-years were examined as a combined measure of duration and dose of exposure to the husband's cigarette smoking. The odds ratios for all cell types of lung cancer combined and for adenocarcinoma of the lung are displayed in Fig. 1. Separate analyses were conducted with each control group for comparison. Because the findings were so similar for each group, the results are presented for the two control series combined (n = 1131). An increasing risk of lung cancer and adenocarcinoma of the lung associated with an increasing level of exposure to the spouse's cigarette smoking was found. The positive trend in risk by pack-years of exposure is statistically significant for adenocarcinoma of the lung ($P < 0.01$). A weaker dose response is observed when all histopathological types of lung cancer are combined (trend, $P = 0.07$).

Exposure to ETS from various sources during adult life was evaluated. The results are summarized in Table 6. For simplicity of presentation, the data in this table also represent the findings using the two control groups combined because the individual results using each control group were entirely consistent. Exposures to cigarette smoking from spouse(s), other household members, on the job and in other activities of adult life ("social") are each associated with an overall 40-60% significant elevation in the risk of adenocarcinoma of the lung. As noted previously for spouse-related exposures, the risk estimates for all lung cancers without regard to cell type tend to be slightly lower than the comparable estimates for adenocarcinoma of the lung. Significant positive trends ($P < 0.05$) in risk of adenocarcinoma of the lung were associated with increasing duration (years) of exposure to cigarette smoke from a spouse, other household members, and social occasions. For adult household exposures from a spouse and others, estimates of risk rose from lowest to highest in the 30 or more years of exposure category; however, trends were not smooth for exposures in occupational and social settings.

No association was found between risk of any type of lung cancer and childhood exposure to cigars, pipes, cigarettes, or all types of tobacco combined. Table 7 presents the estimated relative risks of lung cancer and adenocarcinoma of the lung among nonsmoking women whose father, mother, or other household member smoked during childhood. None differed significantly from unity. Years of exposure and amount smoked were also examined. No significant elevations in risk were found at any level of smoking by household members during childhood.

Discussion

One of the most striking findings of this study is the distribution of the histopathological cell types of lung cancer in a population-based series of cases well screened to determine lifetime nonsmoker status. Seventy-eight % of 359 reviewed eligible cases in this report were classified as adenocarcinomas. This high proportion of adenocarcinomas and the paucity of squamous and small cell carcinomas was consistent across all study

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Table 5 Association between smoking status of spouse(s) and lung cancer risk[a], all lung cancer and adenocarcinoma of the lung

Spouse ever smoked tobacco (by type)	Cases	Colon cancer controls	Population controls	Adjusted odds ratio[a]	
				Colon cancer controls OR (95% CI)	Population controls OR (95% CI)
All lung carcinomas	(n = 420)	(n = 351)	(n = 780)		
Any type of tobacco	294	231	492	1.28 (0.93-1.75)	1.29 (0.99-1.69)
Cigarettes	264	209	441	1.17 (0.87-1.59)	1.20 (0.93-1.55)
Cigars	64	54	97	1.14 (0.76-1.71)	1.26 (0.88-1.80)
Pipe	63	52	110	1.17 (0.78-1.77)	1.21 (0.85-1.72)
Adenocarcinoma	(n = 281)	(n = 351)	(n = 780)		
Any type of tobacco	203	231	492	1.44 (1.01-2.05)[b]	1.47 (1.08-2.01)[b]
Cigarettes	184	209	441	1.31 (0.94-1.84)	1.36 (1.02-1.84)[b]
Cigars	41	54	97	1.05 (0.67-1.66)	1.15 (0.76-1.74)
Pipes	44	52	110	1.16 (0.74-1.82)	1.20 (0.81-1.79)

[a] Adjusted for age (continuous), race (white, black, other), study area (Los Angeles, San Francisco Bay Area, Southern U.S., Atlanta, Houston, and New Orleans), annual family income (<$13,000, $13,000-$34,999, $35,000+), and education (<high school degree, high school degree, some college or higher).
[b] $P < 0.05$.

centers. In the study of Kabat and Wynder (8), a similar proportion (74%) of Krevberg II type tumors was found in their series of 97 nonsmoking females whose self-reported nonsmoking status was confirmed by chart review. In the United States adenocarcinoma is the most common histopathological cell type of primary lung cancer in women, but the proportion of all female lung cancer cases with all subtypes of adenocarcinomas (papillary, acinar, bronchioloalveolar, and solid) is 34% (SEER Public User Tape, 1978-1987).

Our study, in which adenocarcinoma is predominant and is the cell type clearly associated with increased risk from adult ETS exposures, is in contrast to several of the earlier studies of involuntary exposure to ETS. Trichopoulos *et al.* (2) in the initial case-control study of lung cancer and passive smoking among nonsmoking women excluded cases of adenocarcinoma including bronchioloalveolar; however, that study included no histopathological review. They reported an odds ratio from 1.8 to 3.4 associated with the husband's smoking habits. Dalager *et al.* (16) reported a 3-fold elevated risk associated with the spouse's smoking only for squamous and small cell carcinomas and no increased risk of other cell types, of which adenocarcinoma and its subtype, bronchioloal-

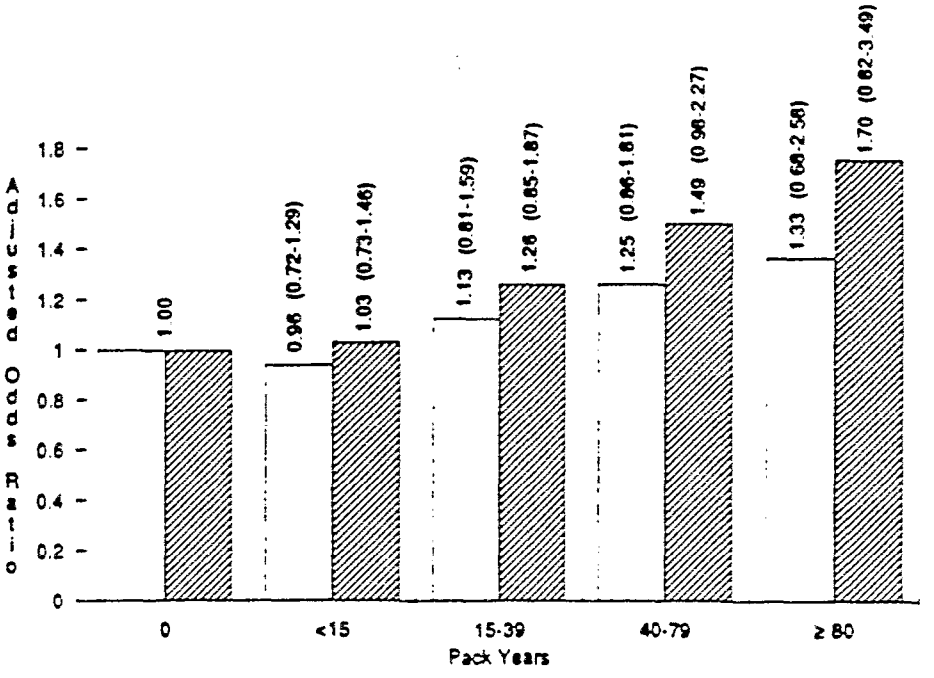

Fig. 1 Adjusted odds ratios for all lung cancer and for adenocarcinoma of the lung associated with pack-years of exposures from spouse(s). □, all lung cancer, trend $P = 0.07$. ▨, adenocarcinoma, trend $P < 0.01$.

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Table 6 Association between risk[a] of lung cancer and adult exposures to cigarette smoke among nonsmoking women

Years of exposure by source	All lung carcinomas adjusted odds ratio[a] (95% CI)	Adenocarcinoma of the lung adjusted odds ratio[a] (95% CI)
Household exposure		
Spouse		
Ever exposed[b]	1.21 (0.96-1.54)	1.38 (1.04-1.82)[c]
0 years	1.00	1.0
1-15	1.19 (0.88-1.61)	1.33 (0.93-1.89)
16-30	1.14 (0.82-1.59)	1.40 (0.96-2.05)
>30	1.25 (0.91-1.72)	1.43 (0.99-2.09)
	Trend $P = 0.14$	Trend $P = 0.03$
Other household members		
Ever exposed[b]	1.23 (0.97-1.56)	1.39 (1.05-1.82)[c]
0 years	1.00	1.00
1-5	1.20 (0.90-1.61)	1.36 (0.98-1.89)
6+[d]	1.23 (0.89-1.69)	1.35 (0.93-1.94)
	Trend $P = 0.12$	Trend $P = 0.04$
Occupational exposure		
Ever exposed[b]	1.34 (1.03-1.73)[c]	1.44 (1.06-1.97)[c]
0 years	1.00	1.00
1-15	1.23 (0.86-1.77)	1.58 (1.05-2.39)[c]
16-30	1.45 (1.05-2.00)[c]	1.42 (0.97-2.07)
>30	1.30 (0.93-1.80)	1.37 (0.92-2.02)
	Trend $P = 0.02$	Trend $P = 0.10$
Social exposure[e]		
Ever exposed[b]	1.58 (1.22-2.04)[f]	1.60 (1.19-2.14)[f]
0	1.00	1.00
1-15	1.34 (0.97-1.84)	1.29 (0.89-1.87)
16-30	2.01 (1.29-3.15)[f]	2.40 (1.47-3.90)[f]
>30	1.65 (0.98-2.80)	1.50 (0.78-2.77)
	Trend $P = 0.0006$	Trend $P = 0.002$

[a] Adjusted for age, race, study area, annual income, and education.
[b] Referent: never exposed.
[c] $P < 0.05$.
[d] Too few subjects exposed 16+ years.
[e] Social exposure is defined as exposure of 2 or more h/week from sources other than occupational and household members, including spouse.
[f] $P < 0.01$.

veolar carcinoma, comprised 46.1% of the total female nonsmoking cases. In the Swedish study of Pershagen *et al.* (35), 57% of 77 female nonsmokers were adenocarcinomas and 31% squamous and small cell carcinomas. The only statistically significant ETS-associated increased risk was for squamous and small cell carcinomas, the cell types with the highest relative risks associated with active smoking. At the present time small numbers of squamous cell and small cell carcinomas in our data set preclude an adequate assessment of risk associated with ETS exposures for these cell types.

The findings of our study lend some support to the mechanism proposed by Wynder and Goodman (36) whereby inhalation of sidestream smoke might primarily increase risk of adenocarcinoma of the lung. They suggested that inhalation of sidestream smoke through the nasal passages would hinder deposition of respirable smoke particulates in the periphery of the lung while gaseous components such as volatile *N*-nitrosamines, formaldehyde, acetaldehyde, or nitrogen oxides, would be likely to reach the deeper part of the lung. Both squamous cell and small cell carcinomas tend to be centrally located, rather than in the periphery of the lung.

Our study found statistically significant elevated risks of adenocarcinoma of the lung among female nonsmokers who had had household ETS exposure or ETS exposure in occupational settings or from other sources. Each of these exposures occurred during adulthood. Exposures during the first 18 years of life were consistently unrelated to the risk of lung cancer.

Any exposure (ever/never) from a spouse who smoked was associated with at least a 30% excess risk. Increasing amount per day and years smoked significantly increased risk. The pattern of risk was the same when cases were compared to colon cancer cases or population controls and was specific for adenocarcinoma of the lung. Findings for all lung cancers combined reflect the association between ETS and adenocarcinoma of the lung diluted by the weak association with other cell types.

The internal consistency of findings with the two control groups suggests that recall bias resulting from having a diagnosis of cancer is not a likely explanation of the observed effect. The possibility remains that nonsmoking lung cancer cases and nonsmoking colon cancer cases are not similarly motivated to remember exposures to the tobacco smoke of others.

The longest duration of exposure to ETS is associated with the greatest elevation in risk, 1.43, for exposure of 30 or more years to a husbands's cigarette smoking. Although significant trends were found for other adult exposures, the dose response was not monotonic; relative risk estimates tended to decline in the longest exposure category. One possible explanation is that recall of quantitative measures of exposure is less reliable for exposures outside the home and for household members other than the spouse. A recent ten-country study was carried out by the International Agency for Research on Cancer designed to validate self-reported recent exposure of nonsmoking women to ETS from any source compared with the urinary concentration of cotinine. Duration of daily exposure to ETS from the husband was the strongest predictor of urinary cotinine (37). Studies by Pron *et al.* (38) and Coultas *et al.* (39) suggest that quantitative measures, particularly for exposures outside the home, are less reliable than categorical measures.

The lack of any association between childhood ETS exposures and lung cancer in our study, as well as the strong, consistent association with exposures during adulthood, contrasts with two recent reports by Janerich *et al.* (22) and Wu-Williams *et al.* (40). Differences in study design may contribute to the discrepant findings. About 25% ($n = 45$) of the 191 cases in the New York study were males, whereas our study was restricted to female cases ($n = 420$) (22). The authors report that there were only small differences between men and women in the amount of exposure to ETS measured by duration. The mean exposure of women to their husbands' tobacco smoke was 16.2 ± 16.7 years, while men had a mean exposure of 13.0 ± 17.0 years from smoking wives. Furthermore, there was a higher correlation between exposure from spouses lifetime ETS exposure for women in the study ($r = 0.51$) than for men ($r = 0.37$). Intensity (dose) of exposure and temporality of exposure from male and female smoker sources may differ considerably. Relatively small differences in dose, temporality, and

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Table 7 Association between risk[a] of lung cancer and childhood[b] exposures to tobacco smoke among nonsmoking women

Ever smoked tobacco	Cases	Colon cancer controls	Population controls	Adjusted odds ratio[a]	
				Colon cancer controls OR (95% CI)	Population controls OR (95% CI)
All lung carcinomas					
Father	196	189	420	0.91 (0.67-1.24)	0.82 (0.64-1.07)
Mother	44	40	97	0.85 (0.53-1.38)	0.84 (0.56-1.26)
Other household member	177	152	327	0.83 (0.59-1.18)	0.96 (0.71-1.29)
Adenocarcinoma					
Father	139	189	420	0.96 (0.69-1.35)	0.89 (0.66-1.19)
Mother	30	40	97	0.91 (0.54-1.55)	0.89 (0.56-1.43)
Other household member	125	152	327	0.81 (0.55-1.20)	0.91 (0.64-1.29)

[a] Adjusted for age, race, study area, annual income, and education.
[b] Childhood is defined as first 18 years of life.

duration in combination may yield more meaningful differences in exposure than that measured by duration alone. The inclusion of males in the New York study, with possibly lower doses of ETS exposure from smoking wives for fewer years and during a more recent time period, may have reduced the relative risk estimates that were not gender specific. A study in northeast China, which was comparable in size to our study, actually found a decreased risk of lung cancer associated with ETS exposures from spouses and a suggestive increased risk associated with paternal smoking (40). As suggested by the authors, these women had heavy exposures to both indoor and outdoor pollutants, which may have obscured any effect of ETS.

The studies which have examined childhood exposures are more limited than those which have focused on tobacco use by spouses, and the overall findings are inconclusive (3, 5, 11-14, 22, 41). Studies of the reliability of recall of ETS exposures suggest that recall of a parent's smoking history is less reliable than that for spouses (38, 39), and this may account in part for inconsistencies between studies. Janerich *et al.* (22) found a 2-fold increased risk associated with 25 or more smoker-years during childhood and adolescence but no increase for childhood exposures of less than 25 smoker-years (OR = 1.09). In most studies which have reported positive associations, the findings have been primarily for maternal ETS exposures in smokers rather than in nonsmokers. Correa *et al.* (5) found a significantly increased risk of lung cancer (OR = 1.36) among smokers whose mother smoked but no increased risk in nonsmokers and no elevated risk associated with the father's smoking. Wu *et al.* (14) reported a nonsignificantly elevated risk of adenocarcinoma of the lung (OR = 1.7) in females, 80% of whom had a history of smoking. Similarly, in a Swedish study of female lung cancer which included primarily smokers, a nonsignificantly elevated risk was associated with maternal (OR = 1.8) but not paternal (OR = 0.8) smoking (42). Other studies have failed to find an increased risk of lung cancer associated with childhood exposures (11, 12, 43). None of these studies examined maternal smoking as distinct from other childhood exposures. Childhood ETS exposures alone may be insufficient to increase lung cancer risk in lifetime nonsmokers but may increase risk in persons exposed transplacentally or during childhood who later smoke themselves (5).

The female lifetime nonsmokers with lung cancer in our study are considerably older than the female lung cancer cases reported in the SEER program, most of whom have actively smoked. This may represent a cohort effect; that is, older women are less likely to have smoked. The age disparity might also reflect possible differences in response among active and passive smokers. The lower dose of ETS might require a longer duration of exposure for pulmonary carcinogenesis.

Although this report represents the findings of the first 3 years of a 5-year study, it is nevertheless the largest case-control study reported to date on this topic. The findings provide additional evidence in favor of a causal relationship between exposure to ETS and lung cancer in women who have never used tobacco themselves. A dose response, not likely due to chance, was apparent for exposure to tobacco smoke during adult life from a variety of exposure sources. The association was specific for both adenocarcinoma of the lung and for all lung cancers combined compared to colon cancer.

Acknowledgments

The authors are grateful for the cooperation of all of the participating hospitals in the five study areas and the many physicians who helped make this study possible. The authors also thank Rafael Jarpa, Youping Lin, Gail Smith, Mahboob Sobhan, and Diego Zavala for programming and analytic support; Laurel Cederquist, Annie Fung, Judy Goldstein, Helen Gregory, and Anne Morse for field supervision; Dr. Nancy J. Haley and Caren Axelrad for directing the urinary cotinine analyses; and the dedicated medical record abstractors and interviewers in each study center.

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JANERICH, D.T., THOMPSON, W.D., VARELA, L.R., GREENWALD, P., CHOROST, S., TUCCI, C., ZAMAN, M.B., MELAMED, M.R., KIELY, M., AND McKNEALLY, M.F., "LUNG CANCER AND EXPOSURE TO TOBACCO SMOKE IN THE HOUSEHOLD," THE NEW ENGLAND JOURNAL OF MEDICINE 323: 632-636, 1990

This study included 191 case-control pairs. The authors matched cases and controls on the basis of whether the interview was conducted directly or with a surrogate respondent; 129 pairs were direct interviews and 62 pairs were interviews with surrogates. Nonsmokers were defined as never having smoked more than 100 cigarettes. Interviews were conducted face-to-face, and all but five of the cases were histologically confirmed. Questions were asked during the interview concerning smoking in the household for each residence in which the subject had lived. The authors calculated smoker-years of exposure based on the number of years the subject lived in each residence multiplied by the number of smokers in that residence. Of the 28 risk estimates presented in the paper, a statistically significant OR was reported for the exposure index of 25 or more smoker-years in childhood and adolescence. This was the only statistically significant risk estimate reported in the study, and was used by the authors to suggest that "approximately 17 percent of lung cancers among nonsmokers can be attributed to high levels of exposure to cigarette smoke during childhood and adolescence."

- Using the 129 case-control pairs interviewed directly, the authors calculated an OR of 0.93 (95% CI 0.55-1.57) for ever having had a spouse who smoked. This risk estimate was not statistically significant.

- The authors wrote that "[w]e found no adverse effects of exposure to tobacco smoke in the workplace." The only odds ratio for workplace exposure presented was for 150 person-years of exposure. This OR was not statistically significant (OR = 0.91, 95% CI 0.80-1.04). The authors stated that the OR indicated "no evidence of an adverse effect of environmental tobacco smoke in the workplace."

- Data on exposure in social settings was also collected. The authors reported a "statistically significant inverse association between environmental tobacco smoke and lung cancer" for the analyses of social exposures.

- When exposure during childhood and adolescence (defined as up to age 21) was analyzed, the authors calculated an OR of 2.59 (95% CI, 1.22-5.49) for 25 or more smoker-years of exposure, based on 113 case-control pairs. Similarly, when the analysis was conducted using all 191 case-control pairs, the OR was 2.07 (95% CI 1.16-3.68).

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LUNG CANCER AND EXPOSURE TO TOBACCO SMOKE IN THE HOUSEHOLD

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Abstract *Background.* The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

Methods. In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case–control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of "smoker-years," determined by multiplying the number of years in each residence by the number of smokers in the household.

Results. Household exposure to 25 or more smoker-years during childhood and adolescence doubled the risk of lung cancer (odds ratio, 2.07; 95 percent confidence interval, 1.16 to 3.68). Approximately 15 percent of the control subjects who had never smoked reported this level of exposure. Household exposure of less than 25 smoker-years during childhood and adolescence did not increase the risk of lung cancer. Exposure to a spouse's smoking, which constituted less than one third of total household exposure on average, was not associated with an increase in risk.

Conclusions. The possibility of recall bias and other methodologic problems may influence the results of case–control studies of environmental tobacco smoke. Nonetheless, our findings regarding exposure during early life suggest that approximately 17 percent of lung cancers among nonsmokers can be attributed to high levels of exposure to cigarette smoke during childhood and adolescence. (N Engl J Med 1990; 323:632-6.)

THE 1972 Surgeon General's report dealt with the health consequences of passive smoking or environmental tobacco smoke for the first time.[1] In 1986 the entire report was devoted to the issue; it concluded that "involuntary smoking is a cause of disease including lung cancer in healthy non-smokers."[2] More than a dozen epidemiologic studies have assessed the relation between passive smoking and lung cancer.[3-17] The findings have ranged from no detectable increase in risk[10,17] to a moderate (about twofold), statistically significant increase.[4-7] Most studies have found only small elevations in risk, which are frequently not statistically significant.[3,8,9] In a meta-analysis of all the available studies in 1986, Wald et al. found a slightly increased risk of lung cancer associated with environmental tobacco smoke.[18]

We undertook the current study in an attempt to clarify further the role of passive smoking in causing lung cancer. In this report we discuss exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers.

METHODS

We conducted a population-based, individually matched case–control study in New York State from 1982 to 1985. The cases were drawn from seven Standard Metropolitan Statistical Areas (Buffalo, Rochester, Syracuse, Utica–Rome, Albany–Schenectady–Troy, Binghamton, and greater New York, excluding the five boroughs of New York City). This geographic area comprises 23 counties, with approximately 125 diagnostic or treatment facilities, and a population base of nearly 10 million people. A special system for the rapid ascertainment of cases of lung cancer was established in these 125 facilities so that patients could be identified and enrolled as soon after diagnosis as possible. All new cases of lung cancer (diagnosed clinically, histologically, or both) were regularly identified at the participating hospitals. The New York State Cancer Registry was checked routinely to identify any cases that might have been missed by the hospital-based reporting system.

Information on smoking was initially obtained from the patients' medical records. All the case patients reported as having never smoked or as former smokers or whose smoking history was unknown were contacted by telephone, and their smoking status was confirmed. To be included as a "case" in the study, a patient had to reside in the 23-county area, be between 20 and 80 years of age, never have smoked more than 100 cigarettes (nonsmokers) or have smoked at some time but not have smoked more than 100 cigarettes in the 10 years before diagnosis (former smokers), and have been given a diagnosis of primary lung cancer between July 1, 1982, and December 31, 1984, that was confirmed on reexamination of the pathological specimens and clinical records. Slides or blocks of tissue were available for all but five of the case patients. All materials were reviewed by investigators who were blinded with respect to the patient's initial diagnosis, smoking history, and other risk factors. Interviews were conducted with 76 percent of the eligible patients or their closest available relatives or friends (surrogates).

Control subjects were individually matched to the patients and were selected by screening the files of the New York State Department of Motor Vehicles. This source of controls was considered appropriate since it was population-based and provided most of the information necessary to perform the matching. A list of potential control subjects for each case patient was selected on the basis of age (within five years), sex, and county of residence. Potential control subjects were contacted by telephone. The first eligible subject who was found to match the case patient in terms of smoking history (nonsmoker or former smoker) and who agreed to participate was enrolled in the study. An additional matching variable considered at the time of data collection was the type of interview — i.e., direct interview with the patient or control subject versus interview with a surrogate respondent. When a surrogate case patient had to be interviewed, we also interviewed a surrogate for his or her matched

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Supported in part by grants (PO1 CA 42101 and RO1 CA 32088) from the National Institutes of Health.

*Deceased.

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control, even when the control subject was available and willing to be interviewed. Further information on the methods used in the study is available elsewhere.[19]

Data were collected for 439 case–control pairs. Of these, 242 pairs were former smokers and 197 pairs had never smoked. Separating the residual effects of direct smoking from those of passive smoking among former smokers involves more complex analytic and interpretational issues than does an examination of the effects of passive smoking in those who have never smoked. This report is therefore limited to persons who never smoked. Six of the 197 pairs who had never smoked were mismatched in terms of the type of interview (direct vs. surrogate) and have therefore been excluded. Thus, the analyses reported here were based on 191 matched case–control pairs. A total of 129 pairs were interviewed directly, and surrogates were interviewed for 62.

All information was collected during a face-to-face interview with use of a precoded questionnaire. Case patients and control subjects were interviewed in exactly the same fashion, and except for items concerning the clinical aspects of the current medical condition, both groups answered the same questions.

Information about smoking in the household was collected separately for each residence in which the subject had lived for one year or more, up to a maximum of 12 residences. The number of "smoker-years" of exposure was calculated by multiplying the number of years the subject lived in each residence by the number of smokers (including the spouse) in that residence. The products for all residences were summed.

Smoking by the spouse was also recorded separately from that by other household members in a subsequent section of the questionnaire. The information consisted of the number of years the spouse had smoked while living with the case patient or control subject and the number of cigarettes smoked per day. Smoker-years of exposure from the spouse's smoking were calculated in the same manner as for the entire household. Pack-years of exposure from the spouse were calculated by multiplying the number of packs smoked per day by the number of years that the spouse smoked while living with the subject. If the subject had been married to more than one smoker, then the numbers of smoker-years and pack-years of exposure for all spouses were summed.

The questionnaire also included sections on exposure to environmental tobacco smoke in the workplace and in social settings outside the home. The format for these questions differed from that used to collect data on exposure in the household. The summary results of this analysis are presented here; detailed findings are available elsewhere.[19]

Statistical techniques appropriate for the analysis of individually matched case–control studies were used.[20] For clarity of presentation, percentages were tabulated for case patients and control subjects separately, rather than for matched pairs. However, odds ratios were computed on the basis of the matched pairs. The conditional logistic-regression model was used in the multivariate analyses.[20] Comparisons of the effects of exposures that occurred during different periods of the subjects' lives were based on evaluation of differences in the magnitude of appropriate logistic-regression coefficients. For statistical testing of these differences, we used the variance–covariance matrix from the logistic-regression analyses.

Results

Smoking by spouses contributed a large proportion of lifetime exposure to environmental tobacco smoke but was not the chief source of exposure. Table 1 shows the amount of exposure to environmental tobacco smoke (expressed in smoker-years) during childhood and adolescence, during adulthood, and from the spouse for the 191 control subjects who had never smoked. There were only small differences between men and women. The spouse contributed about 30 percent of the lifetime smoker-years of exposure; the correlation coefficients for exposure from the spouse and lifetime exposure were 0.37 for men and 0.51 for women. Exposure during childhood and adolescence (<21 years of age) contributed a similar percentage of the lifetime smoker-years but correlated more closely with lifetime exposure (correlation coefficient, 0.92 for men and 0.61 for women). The average lifetime exposure was 46.6 smoker-years for men and 52.7 smoker-years for women. During adulthood, household exposure from sources other than the spouse was somewhat greater than from the spouse.

Table 1. Distribution of Smoker-Years of Exposure to Environmental Tobacco in the Household.*

Category of Exposure	Men	Women
Lifetime smoker-years, mean ±SD	46.6±53.7	52.7±42.9
Smoker-years during childhood and adolescence†		
Mean ±SD	15.4±20.6	16.1±16.2
Percent of lifetime exposure	33.1	30.6
Correlation with lifetime exposure	0.92	0.61
Smoker-years from spouse		
Mean ±SD	13.0±17.0	16.2±16.7
Percent of lifetime exposure	28.0	30.7
Correlation with lifetime exposure	0.37	0.51
Smoker-years during adulthood from sources other than spouse		
Mean ±SD	18.1±31.0	20.5±29.9
Percent of lifetime exposure	38.9	38.9
Correlation with lifetime exposure	0.91	0.83

*Based on 45 male and 146 female control subjects who had never smoked more than 100 cigarettes. Information on smoker-years of exposure from the spouse is for 45 male and 140 female control subjects. Smoker-years were calculated by multiplying the number of years the subject lived in a residence by the number of smokers in the household.

†Less than 21 years of age.

Table 2 shows the odds ratios for developing lung cancer in relation to the degree of exposure to tobacco smoke in the household for the 191 nonsmoking case–control pairs. The data are stratified by levels of exposure (measured in smoker-years) and by the periods of life when the exposure occurred. Exposures during childhood and adolescence were defined as exposures that occurred when the subjects were less than 21 years of age. Exposures during adulthood include all household exposures from 21 years of age to the time of diagnosis. Although the odds ratios for the higher exposure categories are somewhat higher than those for the lower categories, no clear dose–response relation is evident, and most of the 95 percent confidence intervals include 1.0. For exposures in childhood and adolescence, the highest level of exposure is associated with the greatest elevation in risk, and the 95 percent confidence interval excludes the null value (odds ratio, 2.07; 95 percent confidence interval, 1.16 to 3.68). For the 129 case–control pairs who were interviewed directly, the odds ratio for persons with 25 or more smoker-years of exposure in childhood and adolescence was 2.31 (95 percent confidence interval, 1.16 to 4.61).

With smoker-years during childhood and adolescence and smoker-years during adulthood treated as continuous variables and included simultaneously in a logistic model, each increment of five smoker-years of exposure during childhood and adolescence was found to increase the risk of lung cancer by 6.5 percent (95 percent confidence interval, 0.1 to 13.2). On the other hand, each additional five smoker-years of exposure

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Table 2. Relation of Smoker-Years of Exposure to Environmental Tobacco Smoke to the Risk of Lung Cancer among Persons Who Never Smoked More than 100 Cigarettes.*

No. of Smoker-Years	Case Patients	Controls	Odds Ratio (95% CI)
	(no. (%))		
Childhood and adolescence†			
0	57 (29.8)	68 (35.6)	—
1–24	82 (42.9)	94 (49.2)	1.09 (0.68–1.73)
≥25	52 (27.2)	29 (15.2)	2.07 (1.16–3.68)
Adulthood			
0	44 (23.0)	39 (20.4)	—
1–24	37 (19.4)	48 (25.1)	0.64 (0.34–1.21)
25–49	46 (24.1)	50 (26.2)	0.81 (0.45–1.45)
50–74	36 (18.9)	32 (16.8)	1.00 (0.52–1.93)
≥75	28 (14.7)	22 (11.5)	1.11 (0.56–2.20)
Lifetime			
0	32 (16.8)	33 (17.3)	—
1–24	20 (10.5)	27 (14.1)	0.78 (0.36–1.67)
25–49	35 (18.3)	46 (24.1)	0.80 (0.43–1.50)
50–74	44 (23.0)	40 (20.9)	1.19 (0.63–2.27)
75–99	33 (17.3)	21 (11.0)	1.80 (0.83–3.90)
≥100	27 (14.1)	24 (12.6)	1.13 (0.56–2.28)

*Based on 191 matched case–control pairs. CI denotes confidence interval. Odds ratios are shown for a person with the exposure specified as compared with a person with no exposure (0 smoker-years). Because of rounding, percentages do not always total 100.

†Less than 21 years of age.

during adulthood were estimated to have virtually no effect on risk (95 percent confidence interval, −3.3 to +2.8 percent). The difference in the magnitude of the effect between exposure during childhood and adolescence and exposure during adulthood did not achieve statistical significance ($P = 0.12$). On the basis of the distribution of exposure levels during childhood and adolescence among the control subjects and the magnitude of the effect of early exposure, we estimate that approximately 17 percent of all lung cancers in nonsmokers can be attributed to exposure to passive smoke in the household during childhood and adolescence. On the basis of the odds ratios for the 129 case–control pairs who were interviewed directly, approximately 19 percent of lung cancer in nonsmokers appears to be attributable to exposure to environmental cigarette smoke in childhood and adolescence.

Since smoking by the spouse has been the most commonly reported measure of exposure to environmental tobacco smoke in previous studies, we examined exposure from the spouse separately, although exposure to environmental tobacco smoke from the spouse is also included in the results shown in Table 2. The odds ratios for exposure frequently differed according to the type of interview, especially for the data on exposure to a spouse's smoking. Table 3 therefore shows the results of the analyses of exposure to environmental tobacco smoke from the spouse separately for subjects interviewed directly and those for whom surrogates were interviewed. The odds ratio for the development of lung cancer for those who ever had a spouse who smoked, as compared with those who did not, was 0.93 (95 percent confidence interval, 0.55 to 1.57) for those interviewed directly. In terms of smoker-years of exposure to the spouse's smoke, the results show little effect, with an odds ratio of 1.07 for 25 or more smoker-years of exposure (95 percent confidence interval, 0.59 to 1.97). Estimates based on pack-years of exposure from the spouse were similar to those based on smoker-years. For both measures, there was little evidence of a trend according to amount of exposure among those who were exposed.

All analyses were repeated for only the case–control pairs for whom we had complete and internally consistent data for all residences and marriages. Any pair was dropped from these analyses if data were incomplete or missing for either the case patient or the control subject, leaving 113 pairs of nonsmokers. Our purpose was to ensure that our conclusions were not dependent on the particular methods we adopted to handle inconsistencies or missing items in the data set. The findings were similar to those for the entire group of 191 pairs. The odds ratio for exposure to 25 or more smoker-years in childhood and adolescence was 2.59 (95 percent confidence interval, 1.22 to 5.49).

Exposure in the workplace was measured by recording the number of smokers who worked with each study subject during his or her lifetime and the amount of time the subjects spent working with these smokers. These exposures were compared for case patients and control subjects. Estimating the odds ratio as a continuous variable for an equivalent differential of 150 person-years of exposure gave an odds ratio of 0.91 (95 percent confidence interval, 0.80 to 1.04), indicating no evidence of an adverse effect of environmental tobacco smoke in the workplace. Our assessment of smoking in social settings used an untested, semiquantitative index in which the case patient or control subject used a score of 0 through 12 to indicate his or her regular exposure to tobacco smoke in social settings during each decade of life. Cumulative lifetime reported scores ranged from nearly 0 to more than 70. The odds ratio for an increase of 20 in the cumulative score was 0.59 (95 percent confidence interval, 0.43 to 0.81). Our analysis of exposure in social settings with use of this index showed a statistically significant inverse association between environmental tobacco smoke and lung cancer.

Discussion

We found a statistically significant adverse effect of relatively high levels of exposure to environmental tobacco smoke during the early decades of life (up to the age of 21). For those who were exposed to 25 or more smoker-years during their first two decades of life, the risk of lung cancer doubled. This amount of exposure is equivalent to living with more than one smoker throughout childhood and adolescence — a high but not uncommon level of exposure. An exposure of this level was reported for approximately 15 percent of the control group. By contrast, we found no adverse effect of exposure to environmental tobacco smoke during adulthood, including exposure to a spouse who

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Table 3. Relation of Spouse's Smoking to the Risk of Lung Cancer among Persons Who Never Smoked More than 100 Cigarettes, According to Type of Interview.*

VARIABLE	TYPE OF INTERVIEW	
	DIRECT	SURROGATE
	odds ratio (95% CI)	
Ever had a spouse who smoked		
No	—	—
Yes	0.93 (0.55–1.57)	0.44 (0.19–1.02)
Smoker-years of exposure from spouse		
0	—	—
1–24	0.78 (0.41–1.50)	0.33 (0.11–1.05)
≥25	1.07 (0.59–1.97)	0.33 (0.12–0.95)
Pack-years of exposure from spouse		
0	—	—
1–24	0.71 (0.37–1.35)	0.16 (0.04–0.62)
25–49	0.98 (0.47–2.05)	0.68 (0.18–2.60)
≥50	1.10 (0.47–2.56)	0.20 (0.03–1.22)

*Based on 129 case–control pairs interviewed directly and 59 pairs for whom surrogates were interviewed. Three of the 191 pairs were excluded because for one member of the pair there was missing information about whether the subject had a spouse who smoked. Data on smoker-years of exposure were available for 129 case–control pairs with direct interviews and 56 pairs with surrogate interviews. Data on pack-years of exposure were available for 122 pairs with direct interviews and 51 pairs with surrogate interviews. CI denotes confidence interval. Odds ratios are shown for a person with the exposure specified as compared with a person with no exposure to a spouse who smoked.

smoked. Although problems of recall and other potential biases may have influenced the results, our data suggest that exposure in early life may be a limited but important contributor to the risk of lung cancer in nonsmokers. A previous study with a small number of subjects found little evidence of an elevated risk of lung cancer among nonsmokers whose parents had smoked.[14] Children of parents who smoke have been shown to be especially susceptible to respiratory problems that occur soon after exposure to environmental tobacco smoke.[2] This type of susceptibility might initiate changes that eventually lead to lung cancer when the exposed children become adults, but we know of no specific mechanism that would explain our findings.

We found no adverse effects of exposure to tobacco smoke in the workplace, although we did not have enough information about the level of exposure in the workplace to assess the precision of our measurements. The apparent protective effect of exposure in social settings is difficult to explain. During the course of this study, regulations in New York began to restrict smoking in the workplace and in social settings such as restaurants. We did not anticipate this development and cannot estimate how much the awareness of these new restrictions might have affected the responses of the study subjects or their surrogates.

Evidence is clearly mounting that tobacco smoke inhaled passively by nonsmokers is potentially carcinogenic. In a recent study, Maclure et al.[21] found elevated levels of carcinogens in the blood of passive smokers. Levels of hemoglobin adducts of 4-aminobiphenyl and adducts of 3-aminobiphenyl were significantly elevated in subjects with confirmed exposure. The validity of this finding was supported by additional evidence that showed a sharp decline in the levels of adducts among smokers who quit.[21]

At present, information on past exposure to environmental tobacco smoke can be obtained only by interview. The available biologic markers, such as cotinine, cannot be used to confirm exposure that occurred years or decades earlier. The use of interviews to obtain a lifetime history of exposure to passive smoking requires that the questionnaire be structured and the interview techniques be standardized so that all subjects are interviewed in the same way. We took steps to ensure such standardization. Two recent reports may lead to improved ways to measure lifetime exposure to environmental tobacco smoke by means of interviews.[22,23] In one of these studies, which attempted to evaluate the reliability of interview data by repeat interviews, information on exposure during childhood was found to be very reliable.[23]

It was necessary to use surrogate respondents for about one third of the interviews, usually because the patients were too ill to be interviewed. To minimize potential bias, surrogates were also interviewed for the matched control subjects, and separate estimates were calculated for respondents interviewed directly and surrogate respondents. We used equal care in all types of interviews and in all subject areas covered in the interviews; however, the data we obtained in interviews with surrogates still differed somewhat from those obtained in direct interviews. Inaccurate reporting of exposure tends to bias odds ratios toward the null value unless a systematic bias is present. Data from surrogate respondents are likely to introduce random error because of the surrogate's lack of detailed knowledge of the subject's exposure. On the other hand, it is possible that the surrogates for patients with lung cancer might tend to underreport the exposure contributed by their own smoking to a greater extent than surrogates for control subjects. Such a difference could mask an actual increase in risk or reverse the direction of the association. The findings shown in Table 3 indicate that the use of data from surrogates may have led to an underestimation of the effect of exposure from the spouse. Although our results for exposure due to smoking by the spouse differ from those of earlier studies,[18] our findings regarding other types of household exposure support the conclusion that exposure to environmental tobacco smoke can cause lung cancer.

Akiba et al.,[8] Dalager et al.,[9] and Garfinkel[3] have reported elevations in risk of 30 percent, 50 percent, and 10 percent, respectively, associated with exposure to a spouse's smoking; none of these increases were statistically significant. With the exception of Chan et al.[24] and Koo et al.[25] in Hong Kong, these and most other investigators have reported point estimates that suggest an increased risk for those exposed. The duration of exposure, as measured by the number of years the spouse smoked while living with the subject, did not have a statistically significant effect in our data. Two studies that used the same measure

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of exposure also failed to exclude the null value.[8,9] Garfinkel et al.,[7] using a different measure for duration of exposure (husband's smoking in the last 5 and 25 years), found one significant association among the large number examined. Exposure due to smoking by the spouse, expressed in terms of pack-years while the spouse was living with the subject, was found not to be significantly associated with lung cancer. Using a comparable measure of exposure, Trichopoulos et al.[5] reported relatively large increases in risk (greater than twofold). Perhaps our data do not show that smoking by the spouse increased the risk by itself because smoking by the spouse made up only about one third of the subjects' lifetime exposure to environmental tobacco smoke. It is also possible that physical circumstances and differences in study areas, the size of residences, ventilation, and other important physical aspects of the living conditions, as well as social habits that affect exposure within the family, will need to be measured and analyzed before the differences in findings among the studies can be reconciled.

The evidence we report lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

We are indebted to Andreas Nicolaou for his assistance with the computer programming used in our analyses.

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WU-WILLIAMS, A.H., DAI, X.D., BLOT, W., XU, Z.Y., SUN, X.W., XIAO, H.P., STONE, B.J., YU, S.F., FENG, Y.P., ERSHOW, A.G., SUN, J., FRAUMENI, J.F., AND HENDERSON, B.E., "LUNG CANCER AMONG WOMEN IN NORTH-EAST CHINA," BRITISH JOURNAL OF CANCER 62: 982-987, 1990

United States and Chinese researchers collaborated on this large case-control study, conducted in two industrialized cities whose lung cancer rates are among the highest in China. Data were collected by personal interview with 964 cases and 959 controls (the authors do not indicate whether any surrogate respondents were used). Histological information was available for only 42% of the cases. A number of potential confounders, including diet, history of lung disease, and use of traditional heating devices, were examined. Although the authors reported no statistically significant case-control differences regarding several indices of ETS exposure, they nevertheless wrote: "Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognised as a cause of lung cancer around the world." An OR of 0.7 (95% CI 0.6-0.9) was reported for spousal smoking among nonsmoking individuals (205 cases, 331 controls); this OR is statistically significantly negative.

- For nonsmokers reporting ETS exposure in the workplace, the authors reported an odds ratio of 1.1 (95% CI 0.9-1.6). Although the reported OR was not statistically significant, the authors characterized it as "a small excess risk."

- ORs for mother or father smoking were presented. However, it appears that these analyses represented adult rather than childhood exposure. Nonetheless, neither was statistically significant.

- Statistically significantly elevated ORs were reported for the use of indigenous heating devices. For instance, use of "kang," brick beds heated directly by a stove beneath them, for more than 21 years was associated with an OR of 1.5 (95% CI 1.1-2.0).

- Cooking practices were also associated with statistically significant elevated relative risks. For instance, deep frying more than two times per month had a reported OR of 2.1 (95% CI 1.5-2.8), and experiencing frequent eye irritation while cooking had an OR of 1.8 (95% CI 1.3-2.6).

- ORs for certain medical history variables were also statistically elevated. A history of tuberculosis in a household member had an OR of 1.6 (95% CI 1.2-2.1), and

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a history of pneumonia in the home had an OR of 2.3 (reportedly statistically significant, but no CI was given).

The authors claim that their data suggested there was no effect of diet on lung cancer risk. This conclusion is not consistent with data presented in other studies, which suggest that certain dietary variables may be related to lung cancer risk.

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Br. J. Cancer (1990), 62, 982-987

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Lung cancer among women in north-east China

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Summary A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities which have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumours among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to 'Kang' and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung.

The rate of lung cancer among Chinese females is among the highest in the world. Elevated incidence, particularly of adenocarcinoma of the lung, has been noted for Chinese females residing in different geographic areas, including Singapore (Law *et al.*, 1976), Hong Kong (Kung *et al.*, 1984), Shanghai (Gao *et al.*, 1988) and the United States (Hinds *et al.*, 1981). The high rates are unusual because few Chinese women smoke tobacco. Within China, elevated rates of female lung cancer are found in urban areas such as Shanghai and in rural as well as urban areas of the northeastern provinces of Liaoning and Heilongjiang (National Cancer Control Office, 1980; Xu *et al.*, 1986). Reasons for the geographic variation and clustering of high rates of lung cancer in the northern provinces are not known. We report here the results from case-control studies conducted in Shenyang and Harbin, the two major industrial cities in Liaoning and Heilonjiang provinces, to evaluate the role of several potential risk factors.

Methods

In 1985-87, investigators from the Liaoning Province Public Health and Anti-Epidemic Station and the US National Cancer Institute conducted a large lung cancer study including 1,517 males (729 cases, 788 controls) and 1,073 females (518 cases, 555 controls). During the same time period, investigators at Harbin Medical College and the University of Southern California conducted a case-control study focused on female lung cancer (446 cases, 404 controls). Investigators from both studies met during the planning phase of the study and adopted a unified protocol to ascertain and select cases and controls, and a common questionnaire for the interview component of the study. Data on risks from smoking and air pollution among men and women in Shenyang have been published elsewhere (Xu *et al.*, 1989). Herein we report risks among females associated with a variety of factors, increasing sample sizes by nearly 80% by combining information from the two cities.

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Received 27 March 1990; and in revised form 25 July 1990.

Case ascertainment

We sought to enrol all newly diagnosed primary lung cancers in females in the study areas between 1985 and 1987. Utilising the cancer registries of Harbin and Shenyang, a system of rapid case ascertainment was established with the cooperation of all the major hospitals serving its area (about 35 in each city). In brief, the admitting physicians at each participating hospital completed a case abstract form whenever a lung cancer was diagnosed. We received these abstracts on a bi-weekly basis and selected as eligible cases those with primary, incident lung cancers diagnosed among female residents of the study area who were aged less than 70 years at the time of diagnosis. The lung cancer diagnosis and cell-type classification were verified locally in each study area by a panel of pulmonary specialists and pathologists.

Control selection

Controls were females randomly selected from the general populations of Harbin and Shenyang. Controls were frequently matched by 5-year age group to the expected distribution of cases, which was determined in advance using the number and age distribution of female lung cancer cases reported in the two cities in 1983. A three-stage sampling procedure was used to select each control. The initial unit for randomisation was the neighbourhood committee, of which there are about 1,500 each in Harbin and in Shenyang. Committees were randomly selected with replacement after weighting by their population sizes. Then we randomly chose a household group from the approximately 10-25 household groups within each selected neighbourhood committee. In the final stage, among all females in the 5-year age category within the household group, one was randomly selected.

Questionnaire

A structured, pre-coded questionnaire was used by trained interviewers who conducted personal interviews with the participants in their homes or work sites or in the hospital/clinic. The interview gathered information on demographic factors, active and passive smoke exposure, lifetime residential and occupational histories, diet and cooking practices, personal history of noncancerous lung diseases, history of tuberculosis

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(TB) and cancer in first degree relatives, and reproductive factors. Questions on smoking included the amount and types of tobacco products smoked, age when smoking started, and for ex-smokers, age when smoking stopped. To assess passive smoke exposure, we asked about lifetime residential exposure to tobacco smoke from cohabitants, including the amount and duration of exposure from each smoking cohabitant. In addition, we asked if the subject was exposed to passive smoking at each work place. For each residence in which a subject lived for three or more years, we asked in detail about heating and cooking practices, including methods for heating and cooking and types of fuels used. Several questions were asked about 'Kang', brick beds commonly used in the north-eastern part of China, which are heated either directly by a stove underneath them or by pipes connected to the cooking stove. To assess dietary habits 5 years prior to interview, we asked subjects to estimate their frequencies of intake of 33 food items, including staple grains (rice, wheat, maize), soya bean products (bean curd, fermented bean paste), dried peas and beans, animal protein sources (eggs, fish, shellfish, liver, poultry, pork), fermented/salted foods, alcoholic beverages, and fresh vegetables and fruits. Also included were questions on diagnosis by a physician of previous each lung diseases, age at lung disease diagnosis, and if hospitalisation was required. Information on outcome of each pregnancy, age at menarche and at menopause was also elicited. As a quality-control measure, interviews were cassette-recorded for review by a field supervisor.

Statistical methods

The data were edited, coded, keypunched and submitted to computerised range and consistency checks. The statistical analyses were based on multivariate techniques for case-control data (Breslow & Day, 1980). Unconditional logistic regression analyses were used to estimate summary relative risks (RRs) of lung cancer associated with various factors while adjusting for other factors. RRs were calculated for all lung cancer combined and for specific cell types. We present results for squamous cell and oat/small cell cancers combined because we had too few oat/small cell cancers to conduct separate analysis and because these two cell types of lung cancer are more strongly associated with smoking than adenocarcinoma of the lung (Lubin & Blot, 1984). Our analysis for adenocarcinoma of the lung did not include large cell cancers. There were too few large cell cancers for inclusion by cell type. In the analyses including all subjects, the regression models contained terms for age (less than 50, 50–59, 60–69 years), education (no formal education, primary or secondary school, high school and higher), smoking (non-smoker, smoked 1–19 cigarettes per day and 1–29 years, 1–19 cigarettes per day and 30–39 years, 1–19 cigarettes per day and 40+ years, 20+ cigarettes per day and 1–29 years, 20+ cigarettes per day and 30–39 years, 20+ cigarettes per day and 40+ years) and study centre (Harbin versus Shenyang). We also conducted analyses restricted to nonsmokers, deleting the smoking variables in the regression model and adjusting only on age, education, and centre.

Results

All interviews were conducted in 1985–87. At the close of case recruitment, 1,049 eligible patients had been identified by the Harbin and Shenyang cancer registries. Nine-hundred and sixty-four (91.8%) were interviewed, 32 (3.1%) died before our attempted contact, 50 (4.8%) were not located and three (0.3%) refused to participate.

Forty-two per cent ($n = 405$) of the cases were diagnosed by tissue biopsy, 32% ($n = 309$) by cytology, and 26% ($n = 351$) by radiology. Although the percentages of pathologically and cytologically confirmed cases were higher in Shenyang than in Harbin, the cell-type distributions were similar. In the combined set of cases, there were 44% ($n = 310$) adenocarcinomas, 28% ($n = 201$) squamous cell carcinomas, 16% ($n = 117$) oat/small cell carcinomas and the remainder were large cell carcinomas, mixtures of other cell types or the cell type was not known ($n = 66$).

A total of 959 controls (404 in Harbin, 555 in Shenyang) were interviewed. Cases (mean age 55.9 years) and controls (mean age 55.4 years) were closely matched on age but cases were less educated than controls. Relative to those with no formal education, the RRs for women with primary/junior school, high school technical school or college education was 0.9, 1.0, 0.8 respectively (RR for linear trend 0.9; 95% CI 0.8–1.0).

Smoking habits

Table I shows the percentages of women by 5-year age group who smoked cigarettes for 6 months or longer. The prevalence of smoking in the general population (i.e. among controls) varied with age, being much higher (approximately 40%) among women 50 or over than among women below 50 (smoking rate 24%), but increased risks were seen in smokers at all ages. For all lung cancers combined, smokers experienced a 2.3-fold (95% CI 1.9–2.8) increased risk of lung cancer. The age-, education- and city-adjusted RRs for smoking were 4.2 (95% CI 3.0–5.9) for squamous cell cancer, 2.2 (95% CI 1.4–3.2) for oat small cell cancers, 1.5 (95% CI 1.1–1.9) for adenocarcinoma of the lung and 2.5 (95% CI 1.9–3.3) for the 'other' category which included those diagnosed clinically, large cell cancers, and those with mixed or unknown cell type. Most (57%) cases began smoking before they were 20 years old, compared to 40% of controls; the average age when subjects began to smoke was 19.9 for cases and 24.0 for controls. The women were not heavy smokers. Few subjects (9% cases, 4% controls) smoked 20 or more cigarettes per day, and the mean daily number of cigarettes smoked was 8.1 for cases and 6.8 for controls. Nevertheless, there was sufficient variation in amounts smoked to show that risks of lung cancer significantly ($P < 0.001$) increased with increasing numbers of cigarettes smoked per day and with increasing duration of smoking (Table II). Clear independent effects were seen with each measure of smoking exposure within categories of the other, with the associations stronger for squamous/oat cell carcinomas than for adenocarcinoma. At the same level of smoking, 2- to 4-fold differences in the magnitude of the risk between the two cell types were typically observed.

Passive smoking

Table III shows the RRs associated with passive smoke exposure, first among all subjects after adjusting for personal smoking and then among non-smokers. Eighty-eight per cent of all cases and controls reported having lived in at least one of their residences with a cohabitant who was a smoker. There were no significant case-control differences in ever having lived with a smoker, except for non-smokers who lived with a spouse who smoked, where the risk was reduced (RR 0.7; 95% CI 0.6–0.9). The lowered risk associated with a spouse who smoked was seen only in Harbin: 60% of non-smoking controls and 46% of non-smoking cases in Harbin reported that the spouse ever smoked, compared to 52% of non-smoking controls and 52% of non-smoking

Table I Prevalence of smoking by 5-year age groups and corresponding relative risks for lung cancer associated with smoking

	Cases		Controls			
Age (years)	*n*	*% smokers*	*n*	*% smokers*	*RR*	*(95% CI)*
< 50	208	34	163	24	1.6	(1.0, 2.6)
50–54	203	60	196	35	2.7	(1.8, 4.0)
55–59	232	62	241	43	2.0	(1.4, 3.0)
60–64	184	68	191	39	3.2	(2.1, 5.0)
65+	137	60	161	40	2.2	(1.4, 3.5)

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Table II RR and 95% CI for lung cancer associated with intensity of smoking by cell type

Cell type	Cigarettes per day	Duration of smoking (years) 1-29		30-39		>40	
All lung cancer	1-19	1.3 (1.0, 1.7)*	(118/125)†	2.6 (1.9, 3.5)	(146/83)	3.2 (2.4, 4.3)	(187/103)
	≥20	1.8 (0.9, 3.6)	(19/14)	3.3 (1.8, 6.2)	(33/15)	5.7 (2.9, 11.5)	(36/11)
Squamous oat cell	1-19	2.0 (1.3, 2.9)	(48/125)	3.9 (2.6, 5.9)	(56/83)	4.7 (3.1, 7.1)	(64/103)
	≥20	2.0 (0.7, 5.4)	(6/14)	3.8 (1.7, 8.8)	(10/15)	12.0 (5.3, 27.0)	(17/11)
Adenocarcinoma	1-19	0.8 (0.5, 1.3)	(30/125)	1.7 (1.1, 2.5)	(37/83)	2.0 (1.3, 3.0)	(45/103)
	≥20	0.8 (0.3, 2.6)	(4/14)	3.8 (1.8, 8.0)	(15/15)	2.8 (1.0, 7.4)	(7/11)

*95% confidence intervals. †Numbers of cases:controls are in parentheses.

Table III RR for lung cancer associated with passive smoke exposure

Source of passive smoke exposure	Passive smoke exposure	All subjects Case/controls	RR*	Non-smokers only Case/controls	RR†
Any cohabitant	no	112/111		74/87	
	yes	844/842	0.8	343/515	0.7
Spouse	no	398/402		212/271	
	yes	558/551	0.9	205/331	0.7‡
Mother	no	543/595		296/410	
	yes	413/358	1.0	119/192	0.9
Father	no	484/515		235/352	
	yes	472/438	1.0	182/250	1.1
Workplace	no	403/448		187/301	
	yes	563/513	1.2	228/301	1.1

*Adjusted for age, education, personal smoking and study area. †Adjusted for age, education, and study area. ‡$P < 0.05$.

cases in Shenyang. There were no significant trends in risk with intensity (i.e. number of cigarettes smoked by family members) and duration of exposure (i.e. years of smoking by cohabitants), except for an increasing risk associated with increasing intensity of father's smoking in the presence of the index subject.

There was a small excess risk associated with passive smoke exposure at the workplace. For all subjects, the smoking-adjusted RR was 1.2 (95% CI 1.0–1.4). The result was similar for non-smokers (RR 1.1; 95% CI 0.9–1.6). There were no significant dose-response trends associated with years of passive smoke exposure at work.

Heating and cooking practices

Table IV presents RRs associated with duration of use of Kang and other heating devices. Elevated risks were observed for increasing years of use of Kang (particularly when heated by stoves underneath), heated brick walls or floors (i.e. heated by pipes leading from the stoves to the wall or floor), coal stoves and coal burners. On the other hand, decreased risks were observed for increasing years of use of non-coal-burning stoves and central heating. The patterns were generally similar for smokers and non-smokers, and for squamous/oat cell carcinomas and adenocarcinoma. We also examined the risks associated with years when coal, wood, and central heating served as the main fuel for heating. The RRs tended to rise with increasing use of coal and decline with increasing use of wood and central heating, but none of the trends was significant.

Cases more often reported that their homes became smoky during cooking and that they more frequently had irritated eyes during cooking (Table V). There also was a significant trend in risk with increasing number of meals cooked by deep frying, although this method of cooking was not frequently used. The results were similar for squamous/oat cell cancers and adenocarcinoma, and for smokers and non-smokers.

Occupation

Subjects were asked about all jobs in which they had worked 1 or more years, with cases and controls compared in terms

Table IV Relative risk of lung cancer associated with years of use of specific heating devices

Exposure (years)	Case:controls	RR*/95% CI
Kang		
0	25/40	1.0
1-39	384/376	1.4 (0.8, 2.4)
40-49	132/144	1.1 (0.6, 2.8)
50+	415/393	1.6 (0.9, 2.8)
Burning Kangs		
0	677/740	1.0
1-20	106/91	1.2 (0.9, 1.7)
21+	173/122	1.5 (1.1, 2.0)
Coal stoves		
0-20	192/226	1.0
21-40	511/485	1.2 (1.0, 1.6)
41+	253/242	1.3 (1.0, 1.7)
Non-coal stoves		
0	212/183	1.0
1-20	367/340	0.8 (0.6, 1.1)
21-30	259/295	0.7 (0.5, 0.9)
31+	118/135	0.8 (0.5, 1.1)
Heated brick walls/floors		
0	586/651	1.0
1-20	127/98	1.5 (1.1, 2.1)
21+	243/204	1.4 (1.1, 1.9)
Coal burners		
0	525/583	1.0
1-20	258/202	1.2 (1.0, 1.6)
21+	173/168	1.1 (0.8, 1.4)
Central heat		
0	602/573	1.0
1-20	215/200	1.0 (0.8, 1.3)
21+	139/180	0.8 (0.6, 1.0)

*Adjusted for age, education, personal smoking and study area.

Table V Relative risk of lung cancer associated with frequency of deep frying and eye irritation when cooking

	Case/controls	RR* (95% CI)
Deep fry (times per month)		
0	324/403	1.0
1	326/360	1.2 (1.0, 1.5)
2	170/107	2.1 (1.5, 2.8)
3+	121/81	1.9 (1.4, 2.7)
Eye irritation		
never/rarely	647/732	1.0
sometimes	218/163	1.6 (1.2, 1.8)
frequent	89/56	1.8 (1.3, 2.6)

*Adjusted for age, education, personal smoking and study area.

of their employment in 29 job categories. Most (77%) women held at least one job outside the home, but significantly increased risks were observed only for metal smelting work (RR 1.5; 95% CI 1.0–2.1), while a significantly decreased risk was observed for textile workers (RR 0.6; 95% CI 0.3–1.0). The women were also asked if they were exposed to 12 specific dusts, smoke or fumes at work, with from 1 to 16% reporting on-the-job exposures to the 12 pollution items. Cases reported exposure to coal dust (RR 1.5; 95% CI 1.1–2.0) and to smoke from burning fuel (RR 1.6; 95% CI 1.2–2.2) significantly more often.

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Prior lung disease

Table VI lists RRs of lung cancer associated with specific prior chronic lung diseases. Lung diseases that were first diagnosed within three years of lung cancer diagnosis (and a comparable time period for controls) were excluded from the analysis. After adjusting for smoking, history of any prior lung disease was associated with a 50% increased risk (95% CI 1.2–1.8). The excess was greatest for pneumonia (RR 2.1). An increased risk was found for bronchitis and/or emphysema, but the association was limited to squamous/oat cell cancers (RR 1.6) and not found for adenocarcinoma (RR 0.9).

We investigated whether risk of lung cancer varied according to the lag time following the diagnosis of prior lung disease. Earlier detection of chronic bronchitis/emphysema conveyed greater risk. Relative to those with no history of chronic bronchitis/emphysema, the RRs were 1.3, 1.3, and 1.7 respectively for conditions detected 4–10, 11–20, and 21 + years before lung cancer diagnosis. On the other hand, the RRs were higher for more recent diagnoses of pneumonia and TB. The RRs were 2.7, 2.5 and 1.8 respectively for pneumonia, and 2.8, 1.1, and 1.2 for TB first detected 4–10, 11–20 and 21 + years prior to lung cancer diagnosis. The elevated risk associated with TB diagnosed 4–10 years prior to lung cancer was significant; it was observed for both squamous oat cell cancers and adenocarcinoma of the lung, and among non-smokers as well as smokers.

Family history of TB and cancer

We observed a significant 60% (95% CI 1.2–2.1) increased risk associated with TB in a household member, with similar risks for squamous/oat cell cancers and adenocarcinoma. The familial association was seen in smokers and non-smokers, and remained unchanged after adjusting for personal history of TB. The risk associated with family history of TB increased with decreasing age when the index subject was first exposed. After adjusting for smoking, exposures at age <21, 21–30 and >30 conferred risks of 1.7, 1.5 and 1.2 when compared to those with no household TB exposure.

Family history of lung cancer in first degree relatives, reported by 4.5% of the cases, was associated with a significant 80% (95% CI 1.1–3.0) increased risk. There was little difference in risk by cell type or smoking status. The risk of lung cancer was somewhat higher among those with a family history of other cancers (RR 1.4; 95% CI 1.0–2.0), with the excess risk being higher for adenocarcinoma (RR 1.8) than for squamous/oat cell cancers (RR 1.1).

Menstrual and reproductive factors

Table VII presents risks of lung cancer by various menstrual and reproductive factors. There were little or no association with age at menarche, parity, hysterectomy, spontaneous abortion, pregnancy resulting in difficult labour, and use of oral contraceptives. There was a significant 50% (95% CI 1.2–1.8) increased risk associated with history of miscarriage, and cases tended to have a later age at natural menopause although the trend was not smooth.

Table VII Relative risks of lung cancer associated with menstrual and reproductive factors

	Cases/controls	RR* (95% CI)
Age at menarche		
18 +	184/192	1.0
16–17	427/412	1.1 (0.8, 1.4)
14–15	285/276	1.1 (0.8, 1.4)
<14	55/64	0.9 (0.6, 1.4)
Number of children		
<3	193/205	1.0
3–4	319/300	1.1 (0.9, 1.5)
5–6	275/272	1.0 (0.8, 1.4)
7 +	169/174	1.0 (0.7, 1.3)
Age at natural menopause		
<45	77/112	1.0
45–49	373/303	1.7 (1.2, 2.4)
50–54	278/327	1.3 (0.9, 1.8)
55 +	31/28	1.7 (1.0, 3.2)
Positive history of		
Hysterectomy	36/36	1.0 (0.6, 1.6)
Miscarriage	82/126	1.5 (1.2, 1.8)
Spont. abortion	239/218	1.1 (0.9, 1.4)
Difficult labour	76/61	1.3 (0.9, 1.8)
Oral contraceptive	54/68	0.8 (0.5, 1.2)

*Adjusted for age, education, personal smoking and study area.

Dietary factors

The diet of the subjects was dominated by staple grains (median intake among controls = 1,095 times per year), fresh vegetables (1,188 times per year), fermented salted foods (730 times per year), and soya bean products (365 times per year). Less frequent was consumption of animal protein sources (231 times per year), fresh fruits (52 times per year), and peas and beans (12 times per year). Risks of lung cancer in relation to dietary intake are shown in Table VIII. Higher frequencies of intake of vegetables, either those rich or low in carotene content were not significantly protective against lung cancer. The three foods with the highest carotene content in this study population were dried hot red peppers (16.9 mg of carotene per 100 g), dark leafy greens (2.7 mg of carotene per 100 g), and carrots (2.0 mg of carotene per 100 g). Carrots and dried hot red peppers were consumed less often by cases compared to controls, but these items were not frequently consumed (mean intake among controls was 41.4 and 70.0 times per year respectively). On the other hand, cases had slightly higher intakes of the more commonly consumed dark leafy greens (average intake among controls was 163.5 times per year).

Cases reported higher frequencies of intake of animal protein and fresh fruits. Few women (12% cases versus 8% controls) drank alcohol more than once a year, but they showed a significant smoking-adjusted 30% increased risk of lung cancer compared to those who did not drink at all. However, there was no clear trend with increasing alcohol consumption. There were no appreciable differences in dietary patterns for squamous/oat cell cancers versus adenocarcinoma, nor for smokers versus non-smokers.

Table VI Relative risk for lung cancer associated with previous lung diseases

	All lung		Squamous/oat		Adenocarcinoma	
	Cases/controls	RR* (95% CI)	N†	RR*	N†	RR*
Positive history of: chronic bronchitis and/or emphysema	210/137	1.4 (1.2, 1.8)	79	1.6†	46	0.9
pneumonia	66/28	2.1 (1.3, 3.3)	23	2.3†	15	1.6
tuberculosis	103/83	1.3 (0.9, 1.7)	33	1.2	33	1.1

*Adjusted for age, education, personal smoking and study area. †Number of cases with factor. †95% confidence intervals exclude 1.0.

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Table VIII. Relative risk of lung cancer associated with dietary factors

Dietary factor	Intake (times per year)	Case/control	RR[a] (95% CI)
Staple grain	<1095	308/266	1.0
	1095-1146	352/396	0.8 (0.7, 1.1)
	>1146	290/290	0.9 (0.7, 1.2)
Peas and beans	<4	256/241	1.0
	4-15	221/244	0.9 (0.7, 1.2)
	16-52	319/314	1.1 (0.8, 1.4)
	>52	160/152	1.0 (0.7, 1.3)
Soya bean products	<153	232/217	1.0
	153-365	204/266	0.7 (0.5, 0.9)
	366-485	265/250	0.9 (0.7, 1.2)
	>485	255/219	1.0 (0.8, 1.3)
Animal protein	<109	156/238	1.0
	109-230	229/236	1.6 (1.2, 2.1)
	231-442	235/237	1.6 (1.2, 2.1)
	>442	336/241	2.3 (1.7, 3.0)
Fermented/salted foods	<366	234/273	1.0
	366-625	179/154	1.2 (0.9, 1.6)
	626-990	329/306	1.2 (0.9, 1.5)
	>990	214/219	0.9 (0.7, 1.2)
Vegetables[b] low in carotene content	<366	254/251	1.0
	366-547	256/251	1.0 (0.8, 1.3)
	548-730	248/240	1.0 (0.8, 1.3)
	≥731	198/210	0.8 (0.6, 1.1)
Vegetables[c] high in carotene content	<731	201/223	1.0
	731-1095	355/331	1.1 (0.9, 1.4)
	1096-1460	195/197	1.0 (0.8, 1.3)
	≥1461	205/201	0.9 (0.7, 1.2)
Fresh fruits	<19	203/232	1.0
	19-52	209/249	1.0 (0.8, 1.3)
	53-132	256/231	1.4 (1.0, 1.8)
	>132	288/240	1.5 (1.2, 2.0)
Alcohol beverages	0	649/706	1.0
	1-12	110/96	1.3 (0.9, 1.7)
	13-52	81/76	1.0 (0.7, 1.5)
	>52	116/75	1.3 (1.0, 1.8)

[a]Adjusted for age, education, personal smoking and study area. [b]Includes white potato, pale sweet potato, white vegetables, yellow and green gourds. [c]Includes salted vegetables, dark sweet potato, yellow green squash, dark green leafy greens, yellow and light green leafy vegetables, carrots, red peppers, dried hot red peppers, green peas, tomatoes.

Multivariate analysis

The factors found to have a significant effect on risk of lung cancers in univariate analysis were evaluated simultaneously in multivariate unconditional logistic regression analysis. In addition to smoking, the following variables had a significant effect on risk of lung cancer ($P < 0.05$) and they entered the regression model in the order as shown: deep-frying, eye irritation, pneumonia, household tuberculosis, burning Kang, self-reported occupational exposure to burning fuel, passive smoking from any household member and heated brick wall/floor.

Discussion

This population-based case–control study conducted in two large northern Chinese cities revealed that at least 35% of the lung cancers among women can be explained by cigarette smoking. Although this attributable risk is low compared to Caucasian female populations (Lubin & Blot, 1984), it is higher than elsewhere in China (Chan *et al.*, 1979; Gao *et al.*, 1988), mainly because of a higher prevalence of smoking women in this region. Smoking rates among women over age 50 were nearly double those found in Shanghai or nationally in China (Gao *et al.*, 1988; Weng *et al.*, 1987). Furthermore, women in Harbin and Shenyang started to smoke at a relatively young age. As compared to women in Shanghai, where 19% of female smokers in the general population began smoking at age 19 or younger, approximately 40% started at this age in northern China. Hence, even though amounts smoked were low (averaging eight cigarettes per day among the cases), smoking contributes to the elevated rates of lung cancer among northern Chinese women. It also appears to account for the higher percentage (44%) of squamous/oat cell cancers in our study versus 32% and 35%, respectively, in Shanghai and Hong Kong (Gao *et al.*, 1988; Kung *et al.*, 1984). The relatively low mean daily number of cigarettes smoked by these women may explain the lower relative risks of lung cancer among Chinese compared to Caucasian smokers.

We observed no overall association between lung cancer risk and passive smoking. Our results varied by source of passive smoke exposure, however, with non-smoking cases reporting less exposure from spouses (but only in Harbin), more exposure from fathers, and similar exposure from mothers when compared to non-smoking controls. Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognised as a cause of lung cancer around the world (Surgeon General, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighbourhood air pollution (Xu *et al.*, 1989).

Pollution from coal burning seems likely to contribute to north-eastern China's elevated lung cancer rates. Risks increased with increasing years of use of burning Kang and heated brick walls/floors, and we observed weaker but similar trends with use of coal stoves and coal burners. Levels of air pollution have been reported to be high in both Harbin and Shenyang, with both indoor and outdoor wintertime benzopyrene concentrations exceeding standards for cities in the United States by more than 60-fold (Dai *et al.* personal communication; Xu *et al.*, 1989). Coal burning, especially use of a local smoky coal, has also been implicated in the high lung cancer rates reported among women in Xuan Wei County in southern China (Mumford *et al.*, 1987).

The effects of certain workplace exposures on lung cancer resemble those reported in Shanghai (Levin *et al.*, 1987, 1988), including a decreased risk seen in textile workers. The excess risk among women employed in metal smelting is consistent with the three-fold increased risk among men exposed to inorganic arsenic in copper smelting in Shenyang (Xu *et al.*, 1989) and the United States (Lubin *et al.*, 1981). The occupational findings will be presented in more detail in a separate report.

Our findings that cases were more likely to cook food by deep frying and to more frequently report eye irritation when they cooked are consistent with the increased risks associated with exposure to cooking oil fumes in Shanghai (Gao *et al.*, 1987). The association in Shanghai was strongest for use of rapeseed cooking oil, but few women in Harbin or Shenyang used this type of oil, suggesting that vapors from several types of cooking oils may be linked to increased risk. Condensates of both rapeseed and soya bean cooking oil volatiles have been found to be mutagenic (Qu *et al.*, 1986). Further short-term testing of several types of cooking oils is underway to help identify the responsible constituents and provide leads for additional study.

Certain lung diseases may have an aetiologic role in lung cancer development (Gao *et al.*, 1987; Wu *et al.*, 1988). Such an association is of particular importance in China, where the prevalence of chronic lung disease is high. Indeed we found that 35% of the cases and 24% of the controls reported prior chronic lung disease. Like others, we found an excess risk of squamous/oat cell cancers of the lung, but not adenocarcinoma, in association with chronic bronchitis/emphysema. Our finding of a significant increased risk associated with recent diagnosis of TB (i.e. 4–10 years prior to lung cancer) is consistent with results from Shanghai (Zheng *et al.*, 1988).

Our results are supportive of a familial tendency in lung cancers (Cohen *et al.*, 1977; Ooi *et al.*, 1986*a,b*; Skillrud *et al.*, 1987; Wu *et al.*, 1988). Shared environmental exposures, familial aggregation of smoking habits, and/or genetic predisposition may be important. The percentage of cases having

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affected first-degree family members was small (4%). Recent case-control studies in Great Britain (Ayesh *et al.*, 1984) and the United States (Caporaso *et al.*, 1989), however, suggest that genetic traits may influence susceptibility in a sizeable portion of cases. These investigations revealed significantly increased risks of lung cancer associated with the genetically controlled ability to extensively metabolise the drug debrisoquine, a trait affecting 54% of the control population studied in the United States.

We found no strong support for a role of hormonal factors for lung cancer overall or specifically for adenocarcinoma. The cases did tend to experience menopause at later ages, but the trend in risk with age at menopause was not smooth. History of prolonged labour or hysterectomy, which had been suspected as risk factors for adenocarcinoma because of the potential for trauma-associated lung embolism, occurred more frequently among our cases, but the excess risks were not significant since relatively few women were affected. Risk of lung cancer was recently reported to be increased among Chinese women with short menstrual cycle length (Gao *et al.*, 1988), but this variable was not assessed in the current study.

In other countries the risk of lung cancer is generally reduced among those with higher dietary intake of carotenoids (Ziegler, 1989), but our findings are less clear. Cases had slightly higher rather than lower intake of dark green leafy vegetables, the most commonly consumed rich source of carotene. Moreover, in our analysis using a combined index of all vegetables rich in carotene, high frequencies of intake did not confer a significant protective effect. Reasons for the absence of protective effects are not clear. A possible explanation is that three-fourths of the study population ate vegetables high in carotene content at least twice a day so that the nearly uniformly high intake of carotene-containing foods limited variability and hindered detection of an effect. Data on plasma carotene levels from this study population will be important as a more objective measure of their dietary intake. Misclassification of intake also may have dampened trends. We did not have information on portion size and the highest carotene-containing food in this population is dried hot red peppers, usually used as a condiment. In addition, recall of past diet may have been influenced by recent dietary improvements, perhaps more so among cases who may have been given preferential dietary treatment because of their illness.

In summary, this investigation revealed that contrary to *a priori* expectation in China, cigarette smoking is the major cause of lung cancer among women in north-east China and contributes to the area's high rates of mortality from this tumor. Prevention activities should emphasise smoking cessation, while additional study may help clarify the role of indoor and outdoor air pollution, chronic non-malignant lung disease, occupational exposures, familial susceptibility and other factors in the aetiology of lung cancer.

We thank Joan Howland for preparation of the manuscript.

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SUDDEN INFANT DEATH SYNDROME

Background

Unexplained sudden infant deaths were documented as long as 150 years ago. Prior to 1940, these deaths were often attributed to the mother's "overlying" the infant during sleep. After 1940, when fewer infants slept in bed with their mothers, other possible factors began to be examined. (Beal, 1989)

Today, "Sudden Infant Death Syndrome" (SIDS) is the number one cause of death for infants between the first week of life and one year of age. (Pope, 1983) According to the World Health Organization, a number of European nations have reported a SIDS incidence rate of less than one death per 1,000 livebirths. For instance, Hungary has a SIDS incidence rate of .326 per 1,000 livebirths (1990); Poland has a SIDS incidence rate of .007 per 1,000 livebirths (1990); Bulgaria has a SIDS incidence rate of .08 per 1,000 livebirths (1989); and Czechoslovakia has a SIDS incidence rate of .269 per 1,000 livebirths (1988). (WHO, 1991; WHO 1990; WHO 1989) The incidence of SIDS in the United States ranges between one and three deaths per 1,000 livebirths. (Buck, 1990) The peak age for death among SIDS victims is 12 weeks of age. However, some investigators have reported an age distribution with two peaks (at 8-9 and 13-15 weeks). (Little, 1990)

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In 1969, SIDS was defined as "the sudden death of any infant or young child, unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death." (Little, 1990) Some researchers began to worry that the use of such a broad definition was allowing the diagnosis to be misused, resulting in the true cause of death being missed or allowing malpractice to be covered up. In response to these concerns, the U.S. National Institutes of Health met in June of 1989 to revise the definition of SIDS. The new definition is as follows:

> The sudden death of an infant under 1 year of age which remains unexplained after a complete postmortem examination, including an investigation of the death scene and a review of the case history. Cases failing to meet the standards of this definition, including those without postmortem examinations, should not be diagnosed as SIDS. Cases that are autopsied and carefully investigated but which remain unresolved may be designated as undetermined, unexplained, or the like. (Zylke, 1989)

Another author wrote:

> Sudden Infant Death Syndrome (SIDS), crib death, or cot death, as it is often called, is the unexpected and often unexplained death of an infant, usually under six months of age. The infant is put to bed in apparently good health or with a mild upper respiratory infection; there is no suspicion of anything abnormal. The infant is of an age (2 months to 6 months) to sleep through the night and, as a result, is not discovered until the next morning.

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> There appears to be no warning, no struggle, and no outcry of pain. (Pope, 1983)

The official World Health Organization definition of SIDS is "the sudden and unexpected death of an apparently healthy infant between the ages of two weeks to six months." (Puckett, 1986) Because the majority of Eastern European countries are WHO members, it is fair to assume that the WHO definition of SIDS is accepted in these countries.

As John L. Emery, Emeritus Professor of Pediatric Pathology at the University of Sheffield, observed, very little is actually known about this condition. In fact, many researchers are uncertain as to whether there is actually a single type of infant death known as SIDS or whether it is a collective diagnosis that is assigned to many different types of unexplained infant deaths. (Emery, 1989) Emery wrote:

> Questions are now beginning to be asked, including: Is there such an entity as the sudden infant death syndrome or is it a convenient diagnostic dustbin?

The possibility that SIDS is a "subset of unclassifiable postneonatal deaths," rather than a single entity, has apparently been suggested for a long time. (Little, 1990) One author stated:

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> There is a growing conviction among research investigators that the sudden infant death syndrome is not one phenomenon but probably a number of basic mechanisms. (Pope, 1983)

Physiological Mechanisms: Theories

Many theories have been presented regarding the possible physiological mechanism(s) which may lead to the deaths of these infants. However, no theory has yet been identified as the correct one. Victims of sudden infant death syndrome do, however, appear to have a higher frequency of several physiological characteristics than infants dying of other causes. These characteristics include evidence of brain-stem gliosis [an excess of fibrous tissue in the brain-stem region], retention of brown fat around the kidneys, and hepatic erythropoiesis [production of red blood cells in the liver]. (Zielke, 1989) Several authors have also reported an increased immune response in the gastrointestinal and respiratory tracts of SIDS victims. Another author wrote:

> Mechanisms for sudden unexpected infant deaths remain unproven but the possibilities include cardiac arrhythmias, hypoglycemia [low blood sugar], prolonged apnoea [cessation of breathing] from central respiratory control failure, seizure-induced apnoea, prolonged airway obstruction and alveolar atelectasis [incomplete expansion of the alveoli in the lung]. (Southall, 1988)

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The author concluded that "there is at present no confirmed physiological predictor of SIDS."

It has also been debated for a long time whether these infants may be dying of subtle infectious respiratory diseases. Some investigators have reported finding evidence of respiratory syncytial virus infection in a small number of SIDS victims. Other researchers have reported finding no evidence of respiratory infection in infants who died of SIDS.

Epidemiology of SIDS

Epidemiological studies have reported a wide range of different factors that are reportedly associated with an increased risk of SIDS. These factors include (but are not limited to) the prone sleeping position, hyperthermia, low birthweight, multiple gestation, low socioeconomic status, maternal substance abuse, microbial factors (bedding), bottlefeeding, lack of prenatal care, timing of prenatal care, maternal smoking, pregnancy complications, prematurity, gender, race, maternal education, month of birth, method of birth, parity [number of births], age of mother, marital status of parents, crowded living conditions, room slept in (own vs. shared), social environment, prenatal development, DPT immunization, ventilation of room, low Apgar scores [a numerical expression of the condition of a newborn infant, usually determined

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at 60 seconds after birth, being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color], duration of second stage of labor, gestational length, day of the week, and the employment status of the father. However, as one author wrote:

> Epidemiologists, recognizing the uncertainty involved in the diagnosis of SIDS and hence what they count as SIDS, have had to accept the fact that their data lack precision and thus must be interpreted circumspectly. (Peterson, 1988)

Another group of authors wrote:

> In summary, epidemiologic studies have shown that except for the age at which SIDS occurs, no other factor is characteristic enough of the condition to help predict future victims. Instead, we can only recognize certain clinical and socioeconomic characteristics that, although not specific for SIDS victims, appear to carry a higher risk for this fatal outcome. Although the mechanisms for death are still unknown, there is apparently no genetic basis for SIDS and no cause-and-effect relationship between any particular risk factor and SIDS. (Goyco and Beckerman, 1990)

Epidemiologists have attempted, however, to define the profile of the "typical" SIDS infant. One group reported:

> A "disproportionate" number of mothers of SIDS victims are typically multiparous [birth mothers of more than one child], non-white, poor,

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> smokers of lower socioeconomic status, who receive late or no prenatal care in spite of a high frequency of pregnancy problems and deliver a small pre-term infant which is then raised in marginal circumstance until its demise.

However, they also conceded that "these factors alone or in combination fail to account for the majority of SIDS occurrences." (Little, 1990) Similarly, Goyco and Beckerman (1990) wrote:

> A profile of SIDS victims characterizes them as previously healthy babies, usually 2 to 4 months of age, possibly with a history of low birth weight and perinatal complications, who have had a viral infection within the previous 2 weeks and die suddenly and unexpectedly while asleep. Their mothers are likely to be young, poor, uneducated, and in most cases cigarette smokers. However, these characteristics of SIDS infants and their mothers appear to be nonspecific and to carry a poor predictive value, because the majority of SIDS victims do not fit this profile and the vast majority of infants who do will not die of SIDS.

While many theories have been proposed regarding the physiological mechanisms and risk factors for these deaths, we still do not know what causes SIDS. According to several research groups, although there are hundreds of published papers on SIDS, its cause or causes remain unknown. (Kraus, 1989; Pope, 1983; Milner, 1989)

As a 1989 article in JAMA observed:

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A syndrome of apparently healthy infants dying suddenly and inexplicably was described almost a century ago and has been the subject of systematic study for more than 40 years. But understanding of crucial aspects of sudden infant death syndrome (SIDS) -- what causes it, what infants are at risk, and how to prevent it -- is still limited. (Zylke, 1989)

Smith (1991) wrote:

Given the absence of positive evidence indicating the cause of death and faced only with an infant that is suddenly dead, can we really state with confidence that we know of what the infant died? Who are we protecting? Who are we trying to help? More to the point, who are we kidding?

Goyco and Beckerman (1990) wrote:

SIDS remains a threat to the infant population, and for the most part a mystery to the rest of us.

Environmental Tobacco Smoke

There are six epidemiological studies which have reported associations between parental smoking, as an index of exposure to environmental tobacco smoke, and the incidence of sudden infant death syndrome. The first study to report such an association was Steele and Langworth (1966). This study reported that children of smoking mothers were 2.1-3.6 times as likely to die of SIDS as

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were children of nonsmoking mothers. Since 1966, several other authors have reported statistically significantly elevated risks of SIDS associated with exposure to parental (particularly maternal) smoking. (Bergman and Wiesner (1976); Lewak et al. (1979); Malloy et al. (1988); Haglund and Cnattingius (1990); Mitchell et al. (1991))

The major criticism of these studies is that they present no actual exposure data for the SIDS infants. Instead, exposure is based on questionnaire information that is usually obtained from parents. There is no quantitative exposure data in these studies to accurately estimate a SIDS infant's actual amount of exposure to ETS. Without such exposure data, it is impossible to accurately examine the potential relationship between exposure to ETS and the incidence of SIDS.

A second problem with these studies is that even though some of the studies control for several potential confounding factors, other studies control for none or very few of the factors. It has been reported that maternal smoking is associated with such factors as low socioeconomic status, dietary patterns, maternal education, maternal age, etc. Because these other factors have also been reported to be associated with an increased incidence of SIDS, it is critical that they are adequately controlled for in any study which purports to examine the potential relationship

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between maternal smoking and the incidence of SIDS. Unfortunately, this is most often not the case.

Finally, it must again be stressed that a physiological mechanism for SIDS has not been determined. It seems to be premature to attempt to implicate isolated factors as being causally related to SIDS when, in actuality, we do not even know what SIDS is.

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Specific Claims Regarding Maternal Smoking

Claim: **Maternal smoking, both during pregnancy and after birth, may increase the risk of an infant dying of SIDS.**

Response: Theories continue to be proposed regarding the mechanism involved in sudden unexplained infant deaths; however, the cause of SIDS remains unknown. Therefore, no one is certain about what a SIDS death actually consists of physiologically, and, as a result, it is extremely difficult to isolate any one factor as a possible cause.

Several authors have reported that maternal smoking is one of the factors that often appear on a SIDS infant's profile. However, these authors have conceded that maternal smoking carries a poor predictive value for SIDS and that "the majority of SIDS victims do not fit this profile and the vast majority of infants who do will not die of SIDS."

In a letter to Mr. Robert Flaak, the Assistant Staff Director of the Science Advisory Board Staff Office of the United States Environmental Protection Agency, Professor Milan Samanek, M.D., outlined several

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interesting points regarding the claimed association between maternal smoking and SIDS. This letter was in response to the United States Environmental Protection Agency's Revised Draft Risk Assessment on ETS (May 1992), which claims that maternal smoking (during pregnancy and after birth) may be associated with an increased incidence of SIDS. Dr. Samanek first pointed out that "there is an increasing incidence of SIDS in developed countries whereas these countries have a declining rate of smoking." In addition, he stated that "there are regional trends in the incidence of SIDS within a community where the smoking rate is relatively constant." He cited Kahn (1988) as concluding that "[t]he effect of cigarette smoke breathed in by babies has been mentioned but never proven."

Dr. Samanek asserted that an informal review of the literature on SIDS revealed 71 factors unconnected with smoking that may be associated with SIDS. Dr. Samanek stated that the Cnattingius (1990) study cited by the EPA claims a differential effect of maternal smoking on "early" and "late" SIDS. Dr. Samanek suggested that "if this is a passive smoking effect, there should be no difference between these groups; however, if the

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relationship is with pre-natal smoking, why are there no cases of SIDS in the first week of life?"

Finally, Dr. Samanek reported that the epidemiological studies of the possible association between maternal smoking and SIDS do not report actual exposure data for SIDS victims. Instead, the studies rely solely upon questionnaire reports of maternal smoking habits. Dr. Samanek stated that "in my opinion, it is impossible to discuss associations with passive smoking and any disease or dose-response relationships without an exposure measurement."

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Claim: The United States Environmental Protection Agency's Risk Assessment on ETS concluded that maternal smoking is associated with an increased incidence of SIDS.

Response: While the authors of the Draft Risk Assessment claimed an association between maternal smoking and an increased risk of SIDS, the Scientific Advisory Board panel members suggested that the authors could mention SIDS, but strongly recommended against including it in Chapter 8 on actual risk assessment. (Unofficial Transcripts, 1992) Several of the SAB members felt uncomfortable with the discussion of SIDS because of the general lack of knowledge about the condition. The Risk Assessment presented no original data but only reviewed some of the literature available on SIDS. The studies that the Risk Assessment relied on reported no actual exposure data for the SIDS infants and relied instead upon questionnaire information regarding maternal smoking habits. The EPA Risk Assessment fails to provide a comprehensive review of the scientific literature available on SIDS.

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Claim: The Report of the Royal College of Physicians entitled "Smoking and the Young" claims that there is a relationship between maternal smoking and sudden infant death syndrome.

Response: The authors of this Report present no original data but review a select sample of the available literature on SIDS. Although there are over 100 published studies available on SIDS, the Report discusses only three or four studies. The Report fails to discuss the enormous body of literature which suggests that, because of the unknowns involved in SIDS, it is virtually impossible to implicate a single factor as being causally associated with SIDS. Once again, actual exposure data for SIDS infants are not provided in the epidemiological studies cited by the Royal College of Physicians in the Report.

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SUDDEN INFANT DEATH SYNDROME

* Very little is actually known about "sudden infant death syndrome." In fact, many researchers are uncertain as to whether there is actually a single type of infant death known as SIDS or whether it is a collective diagnosis that is assigned to many different types of unexplained infant deaths. (Emery, 1989; Little, 1990; Pope, 1983)

* An informal review of the epidemiologic literature on SIDS revealed 71 factors unconnected with smoking that may be associated with an increased risk of SIDS. (Samanek, 1992)

* No factor that has been associated with an increased risk of SIDS in the epidemiological literature is characteristic enough of SIDS to help predict future victims. One group of authors wrote that "no cause-and-effect relationship" exists between any particular risk factor and SIDS. (Goyco and Beckerman, 1990)

* According to several research groups, although there are hundreds of published papers on SIDS, its cause or causes remain unknown. (Kraus, 1989; Pope, 1983; Milner, 1989)

* The epidemiological studies purporting to show a relationship between maternal smoking and SIDS present no quantitative exposure data. The studies instead rely upon retrospective answers given by parents. The accuracy of this type of information as a surrogate for actual exposure data has been strongly questioned in the scientific literature.

* Even the lead author of a National Center for Health Statistics SIDS study (Schoendorf et al., 1992) which recently reported a two-fold increase in risk for infants passively exposed to tobacco smoke after birth and a three-fold increase in risk for infants exposed both in utero and passively after birth, has been quoted as saying, "From this data, we have a fairly strong association but because of limitations of the data, we can't say there is a cause-and-effect relationship here." (Kansas City Star, December 5, 1992, page A-9)

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POINTS REGARDING THE 1992 NCHS SIDS STUDY

* The lead author of the NCHS study has been quoted as saying, "From this data, we have a fairly strong association but because of limitations of the data, we can't say there is a cause-and-effect relationship here." (Kansas City Star, December 5, page A-9)

* The methods used to estimate exposure to tobacco smoke in this study are not accurate methods. The mothers filled out a survey of approximately 200 questions, an average of 19 months after the birth for case infants and an average of 17 months after the birth for control infants. The question used to estimate exposure to parental smoking after birth was, "On the average, how many cigarettes do you smoke a day now?" The number of cigarettes a mother smokes as long as 18-19 months after the unexplained death of her infant is not necessarily the same as she smoked while the infant was still living. The authors themselves concede that their data "do not allow the determination" of such factors. The authors also concede that the accuracy of the self-reported data used to estimate exposure "is a concern."

* Apparently, the only major potential confounding variables controlled for in this study were maternal age, level of maternal education and marital status. There are many more potential confounding variables (such as sleeping position, type of feeding, etc.) which should have been controlled for.

* According to several research groups, although there are hundreds of published papers on SIDS, its cause or causes remain unknown. Even the authors of the present study concede that, "Although many theories have been proposed to explain the etiology of SIDS, an underlying cause for SIDS has not been identified."

* Researchers have questioned whether there is actually a condition known as SIDS or whether SIDS is actually a collective diagnosis assigned to many different types of unexplained infant deaths. The authors of the present study concede that, "As with any analysis of SIDS, this study is limited by the inherent difficulties in accurately identifying a death from SIDS."

* In the NCHS study, different relationships were found for black and white infants between the smoking of other household members and the risk of SIDS. Why should this be the case if there is a true relationship between amount of exposure to ETS and the risk of SIDS?

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* The authors of the study write:

> To demonstrate a causal relationship between maternal smoking after pregnancy and SIDS death, it is necessary to determine that the mother spent a substantial amount of time with, and smoked cigarettes near, the infant. Unfortunately, the NMIHS lacks the detailed information necessary to make those determinations.

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Relationship of Sudden Infant Death Syndrome to Maternal Smoking During and After Pregnancy

Kenneth C. Schoendorf, MD, MPH, and John L. Kiely, PhD

ABSTRACT. Sudden infant death syndrome (SIDS) is associated with maternal smoking during pregnancy. However, the relationship between tobacco exposure during infancy and SIDS is unknown. The examination of infants whose mothers smoked only after pregnancy will help determine the relationship between passive cigarette exposure during infancy and SIDS risk. This case-control analysis used data on normal birth weight (≥2500 g) infants included in the National Maternal and Infant Health Survey, a nationally representative sample of approximately 10 000 births and 6000 infant deaths. Infants were assigned to one of three exposure groups: maternal smoking during both pregnancy and infancy (combined exposure), maternal smoking only during infancy (passive exposure), and no maternal smoking. SIDS death was determined from death certificate coding. Logistic regression was used to adjust for potentially confounding variables. Infants who died of SIDS were more likely to be exposed to maternal cigarette smoke than were surviving infants. Among black infants the odds ratio was 2.4 for passive exposure and 2.9 for combined exposure. Among white infants the odds ratio was 2.2 for passive exposure and 4.1 for combined exposure. After adjustment for demographic risk factors, the odds ratio for SIDS among normal birth weight infants was approximately 2 for passive exposure and 3 for combined exposure for both races. These data suggest that both intrauterine and passive tobacco exposure are associated with an increased risk of SIDS and are further inducement to encourage smoking cessation among pregnant women and families with children. *Pediatrics* 1992;90:905-908; *sudden infant death syndrome; smoking.*

ABBREVIATIONS. SIDS, sudden infant death syndrome; NMIHS, National Maternal and Infant Health Survey; OR, odds ratio.

The term sudden infant death syndrome (SIDS) describes the unexpected and unexplained death of an apparently well infant. After congenital anomalies, SIDS is the most common cause of infant death in the United States and it is the leading cause of death among infants older than 1 month of age.[1] Approximately 85% of SIDS deaths occur among normal birth weight infants.[2-4]

Although many theories have been proposed to explain the etiology of SIDS, an underlying cause for SIDS has not been identified. There are, however, a number of factors consistently associated with an elevated risk of SIDS.[5] Among the strongest of those factors is maternal cigarette smoking during pregnancy. Past studies have consistently shown a two- to fourfold higher risk of SIDS among infants whose mothers smoked during pregnancy compared with infants whose mothers did not smoke, even after control for other risk factors.[2,3,6-8]

Most hypotheses regarding the association between maternal smoking and SIDS address the possible effects of maternal smoking during pregnancy on fetal oxygenation and fetal development.[6] Several studies also discuss the possibility of an infant's exposure to tobacco smoke after birth playing a role in the smoking-SIDS relationship,[2,9,10] but little evidence exists in support of this hypothesis. Evidence of associations between passive smoke exposure and childhood illness, particularly respiratory disease,[11,12] raises further questions regarding the possible role of postnatal smoke exposure in SIDS risk.

Using data from a national survey on maternal and infant health, we examined the relationships between prenatal and postnatal exposure to tobacco smoke and SIDS risk. Two specific questions were asked: (1) Are infants whose mothers smoke both during and after pregnancy at higher risk of SIDS than those whose mothers do not smoke? (2) Are infants whose mothers smoke only after pregnancy at higher risk of SIDS than those whose mothers do not smoke?

METHODS

A case-control analysis was performed on data from the 1988 National Maternal and Infant Health Survey (NMIHS), a study carried out by the National Center for Health Statistics.[13] The NMIHS is a nationally representative survey of approximately 10 000 live births, 4000 fetal deaths, and 6000 infant deaths that occurred in the United States in 1988.[14] Only the birth and infant death cohorts of the survey were used in this analysis. The sampled live births were chosen randomly within each of six strata defined by birth weight and race, to provide an overrepresentation of low birth weight and black infants. The infant death sample consisted of a simple random sample of all infant deaths occurring in the United States.

For all infants in the NMIHS, retrospective data concerning the pregnancy and infancy were collected on a survey questionnaire completed by the mother. The survey consisted of approximately 200 questions addressing parental and family characteristics, maternal health, and infant health. Standard birth certificate information is also available for all infants in the NMIHS. Additionally, death certificate information is available for infants in the death cohort.

Only infants born to black non-Hispanic or white non-Hispanic mothers were included in this analysis. The sample size of infants of other races or ethnicities was too small to allow meaningful comparisons. Because black and white infants were sampled inde-

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Received for publication May 4, 1992; accepted Jun 22, 1992.
A portion of this work was presented at the 32nd Annual Meeting of the Ambulatory Pediatric Association, Baltimore, MD, May 1992.

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pendently in the NMIHS analyses were performed separately for black infants and white infants.

A case was defined as an infant of normal birth weight (≥2500 g) reported to have died of SIDS (*International Classification of Diseases, 9th Revision, Clinical Modification* underlying cause of death code 798.0), with an autopsy reported on the death certificate. Approximately 92% of both black and white, normal birth weight infants with SIDS coded on the death certificate had an autopsy. Infants of low birth weight were excluded because those infants are at higher risk of death from all causes, which may lead to differential classification of SIDS by birth weight. Additionally, as mentioned earlier, previous population studies have shown that the majority of SIDS deaths occur in normal birth weight infants.[2-4]

To determine whether the relationship between smoking and SIDS simply reflects an association between smoking and infant mortality in general, infants who died of causes other than SIDS made up a second case group. That group consisted of all normal birth weight infant deaths in the NMIHS that did not meet the case definition for SIDS, including those infants reported to have died of SIDS but without a recorded autopsy.

The control group consisted of normal birth weight infants in the NMIHS live birth cohort. In this group, approximately 98% of the questionnaires were completed after the infant was 9 months old. Inasmuch as more than 75% of SIDS deaths occur before 6 months of age,[4,5,8] the likelihood that a control infant would subsequently die of SIDS was minimal.

Tobacco exposure was determined from survey questions regarding maternal smoking habits during pregnancy and at the time the questionnaire was completed. Two questions were used to establish the smoking pattern of an infant's mother: "On the average, how many cigarettes did you smoke a day after you found out you were pregnant?" "On the average, how many cigarettes do you smoke a day now?"

Each infant was placed in one of three exposure groups based on the maternal smoking pattern. The nonexposed group was defined as infants whose mothers did not report cigarette smoking either during pregnancy or at the time of the survey. The passive exposure group consisted of infants whose mothers reported smoking at the time of the survey but not during pregnancy. The combined exposure group included infants whose mothers reported smoking both during pregnancy and at the time of the survey. A small number of mothers reported smoking during pregnancy but not at the time of the survey. Infants of those mothers were excluded from the study because their numbers were insufficient for meaningful analysis. Infants with missing maternal smoking information (fewer than 1% of white case infants and control infants and fewer than 3% of black case infants and control infants) were also excluded.

The smoking habits of other household members were examined to explore more fully the relationships between passive tobacco smoke exposure and SIDS risk. Information was limited to the number of additional household members reported to have smoked at the time of the survey and was dichotomized into none vs any.

The potential confounding effects of maternal age in years (<20, 20 through 24, 25 through 29, >29), maternal education (less than high school, high school graduate, some college, college graduate), and marital status (married at the time of birth vs unmarried) were controlled for in a logistic regression model.[15] Data for those variables were derived primarily from birth certificate information. For individuals with missing birth certificate information, data were obtained from survey responses.

RESULTS

Two hundred one black infants and 234 white infants met the criteria for inclusion as a SIDS death. The control groups consisted of approximately 3000 infants of each race (Table 1). The mean interval between birth and completion of the survey was approximately 19 months for case infants and 17 months for control infants. There was little variation between blacks and whites regarding the interval between birth and survey completion.

Infants who died of SIDS were more likely to have been exposed to tobacco smoke than the control infants, for both races (Table 1). For black infants the odds ratio (OR) was 2.4 for passive exposure and approximately 3 for combined exposure. Passively exposed white infants had an OR of 2.2, while the OR for the white combined-exposure group was slightly greater than 4.

Black infants in both exposure groups had elevated ORs for death from causes other than SIDS, but those ORs were considerably lower than those for SIDS death (Table 1). White infants who died of causes other than SIDS were not substantially more likely to be exposed to tobacco smoke than white survivors.

The ORs for SIDS among black infants in either exposure group did not change markedly after adjustment for the potentially confounding effects of maternal age, education level, and marital status (Table 2). The ORs for white infants decreased after adjustment, to 1.8 for passive exposure and 3.1 for combined exposure. For both races, SIDS was associated with lower maternal age and lower maternal education levels. Marital status was not associated with SIDS after adjustment for the other factors.

The influence on SIDS of the smoking habits of other household members at the time of the survey was examined separately within each exposure group, as well as in the total study population. This analysis revealed differing relationships for black and white infants (Table 3). Among black infants, there was no association between the smoking habits of other household members and SIDS, regardless of maternal smoking pattern. Among white infants, the ORs describing the association between the smoking of other household members and SIDS were elevated for each exposure group but were not statistically significant. The unadjusted ORs ranged from 1.3 in the nonexposed group to 1.6 in the passive exposure group, but the number of cases in each group was small. Combining the exposure groups and adjusting for type of tobacco exposure yielded an OR of 1.4 for the association between SIDS and the smoking of other household members, among white infants. Adjustment for maternal age, education, and marital status slightly lowered the ORs for both black and white infants but did not substantially change the smoking-SIDS relationship (data not shown).

The mean number of cigarettes smoked per day by the mother at the time of the survey was examined to compare levels of postnatal tobacco exposure in the passive and combined exposure groups. Mothers of infants in the passive exposure group reported smoking fewer cigarettes than those in the combined exposure group for both races (Table 4). Within exposure groups, mothers of case infants and control infants reported similar amounts of tobacco use. Additionally, white mothers reported heavier smoking than did black mothers for both exposure groups.

DISCUSSION

Examination of the nationally representative NMIHS allows for more detailed analysis of the association between maternal smoking and SIDS than has been possible with previous population-based data.[2,3] By using the NMIHS, the temporal pattern

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TABLE 1. Odds Ratios for D[illegible] Among Infants Weighing ≥2500 Grams at Birth, Tobacco Exposure

	Black			White		
	Cases	Controls	OR*	Cases	Controls	OR*
Sudden infant death syndrome						
None†	103	2423	Ref	89	1967	Ref
Passive‡	26	255	2.40 (1.49, 3.83)	20	199	2.22 (1.29, 3.78)
Combined§	72	576	2.94 (2.12, 4.07)	125	678	4.07 (3.03, 5.48)
Other causes						
None†	304	2423	Ref	426	1967	Ref
Passive‡	48	255	1.50 (1.06, 2.11)	42	199	0.97 (0.68, 1.40)
Combined§	105	576	1.45 (1.13, 1.86)	182	678	1.24 (1.02, 1.51)

* OR, odds ratio; 95% confidence intervals in parentheses.
† None = mother did not smoke either during pregnancy or after infant's birth.
‡ Passive = mother smoked after infant's birth but not during pregnancy.
§ Combined = mother smoked both during pregnancy and after infant's birth.

TABLE 2. Adjusted Odds Ratios* for Sudden Infant Death Syndrome Among Infants Weighing ≥2500 Grams at Birth

	OR (95% CI)†	
	Black	White
Tobacco exposure		
None‡	Ref	Ref
Passive§	2.33 (1.48, 3.67)	1.75 (1.04, 2.95)
Combined‖	3.06 (2.19, 4.29)	3.10 (2.27, 4.24)
Marital status		
Married	Ref	Ref
Unmarried	0.92 (0.65, 1.32)	1.12 (0.78, 1.59)
Maternal age		
<20 y	2.35 (1.33, 4.15)	1.74 (1.03, 2.94)
20–24 y	1.72 (1.03, 2.86)	1.58 (1.05, 2.39)
25–29 y	1.50 (0.88, 2.54)	1.35 (0.90, 2.01)
>29 y	Ref	Ref
Maternal education		
<High school	2.13 (0.92, 4.94)	2.07 (1.16, 3.68)
High school graduate	1.27 (0.56, 2.87)	1.19 (0.72, 1.98)
Some college	1.27 (0.54, 2.98)	1.08 (0.63, 1.84)
College graduate	Ref	Ref

* The odds ratio for each covariate is adjusted for all the other covariates in the model.
† OR, odds ratio; 95% confidence intervals in parentheses.
‡ None, mother did not smoke either during pregnancy or after infant's birth.
§ Passive, mother smoked after infant's birth but not during pregnancy.
‖ Combined, mother smoked both during pregnancy and after infant's birth.

TABLE 3. Odds Ratios for Sudden Infant Death Syndrome Among Infants Weighing ≥2500 Grams at Birth, by Smoking of Household Members at Time of Survey and Infant's Tobacco Exposure

	OR (95% CI)*	
	Black	White
No exposure†		
Other household smokers		
No	Ref	Ref
Yes	1.00 (0.62, 1.58)	1.33 (0.77, 2.27)
Passive exposure‡		
Other household smokers		
No	Ref	Ref
Yes	1.03 (0.43, 2.47)	1.63 (0.58, 4.74)
Combined exposure§		
Other household smokers		
No	Ref	Ref
Yes	0.83 (0.48, 1.41)	1.42 (0.93, 2.18)
All infants‖		
Other household smokers		
No	Ref	Ref
Yes	0.93 (0.68, 1.27)	1.41 (1.04, 1.90)

* OR, odds ratio; 95% confidence intervals in parentheses.
† No exposure, mother did not smoke during pregnancy or after infant's birth.
‡ Passive exposure, mother smoked after infant's birth but not during pregnancy.
§ Combined exposure, mother smoked both during pregnancy and after infant's birth.
‖ Adjusted for infant's tobacco exposure group.

TABLE 4. Mean Number of Cigarettes Smoked per Day at Time of Survey, by Exposure Group

	Black		White	
	Cases	Controls	Cases	Controls
Passive exposure*	6.8	7.5	12.5	9.9
Combined exposure†	13.0	12.2	20.3	18.9

* Passive exposure, mother smoked after infant's birth but not during pregnancy.
† Combined exposure, mother smoked both during pregnancy and after infant's birth.

and quantity of maternal smoking can be considered, instead of a single yes/no response regarding smoking during pregnancy. These data suggest that exposure to tobacco smoke only after birth, without prior fetal exposure, is independently associated with an increased risk of SIDS. Additionally, this analysis adds to the literature that reports a strong relationship between maternal smoking during pregnancy and risk of SIDS.

As with any analysis of SIDS, this study is limited by the inherent difficulties in accurately identifying a death from SIDS. Limiting the study to normal birth weight (≥2500 g) infants may have decreased misclassification of cause of death by excluding low birth weight infants, who are at high risk of death from all causes and may be more likely to be wrongly classified as having died of SIDS. Additionally, maternal smoking during pregnancy is associated with elevated risks of both low birth weight and infant mortality in general.[16,17] In restricting this analysis to normal birth weight infants, the intent was to measure the association of maternal smoking with SIDS independently of the association of maternal smoking with low birth weight and overall infant mortality.

The accuracy of self-reporting of smoking habits is a concern. However, the percentages of women who

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reported that they smoked during and after pregnancy in the NMIHS are similar to those in analyses of nationally representative National Health Interview Survey data.[18] This concurrence is true for both the combined and passive exposure groups in this analysis.

Bias may have been introduced into this analysis through differential reporting of smoking habits by mothers of case and control infants. It is possible that mothers who smoked and whose infants died of SIDS were less likely to report smoking than were mothers who smoked and whose infants survived. Differential reporting of this type would cause the ORs to be lower than they should be, thus yielding conservative estimates of the strength of the association between maternal smoking and SIDS. Conversely, it is possible that mothers who smoked and whose infants died of SIDS were more likely to report smoking than were mothers who smoked and whose infants survived. This reporting bias would artificially strengthen the association between maternal smoking and SIDS. However, in a recent methodologic study, associations between SIDS and a number of risk factors were not due solely to differential reporting between cases and controls, although smoking was not examined.[19] Additionally, since in our study the association between maternal smoking and death from causes other than SIDS differed from the association between smoking and SIDS death, it is unlikely that the reported relationships between smoking and SIDS are due primarily to differential reporting. Also, within exposure groups, cases and controls reported similar numbers of cigarettes smoked, suggesting that there is no preferential reporting of smoking by outcome.

The pattern of maternal smoking used to define the passive exposure group in this study, smoking after, but not during, pregnancy, is somewhat unusual at first glance. However, smoking cessation during pregnancy with recidivism after pregnancy is a recognized pattern.[18] In the NMIHS data, of those women who reported smoking after, but not during, pregnancy, more than two thirds of white mothers and approximately one half of black mothers reported smoking in the 12 months prior to delivery. Unfortunately, the NMIHS data do not allow the determination of either the stage of pregnancy when those mothers stopped smoking or the age of the infants at the time those mothers resumed smoking.

To demonstrate a causal relationship between maternal smoking after pregnancy and SIDS death, it is necessary to determine that the mother spent a substantial amount of time with, and smoked cigarettes near, the infant. Unfortunately, the NMIHS lacks the detailed information necessary to make those determinations. Additionally, knowledge of the smoking habits of other people having substantial contact with the infants is necessary to truly estimate the effect of passive smoke exposure on SIDS risk. The association between the smoking of other household members and SIDS was different for blacks and whites in this study. Further research is needed to determine whether those are true differences or are due to the limited nature of that information in NMIHS. Despite these limitations, we found a substantial relationship between SIDS and maternal smoking only after pregnancy, even after factors associated with both smoking and elevated SIDS risk were adjusted. This association between passive tobacco smoke exposure during infancy and SIDS risk should be examined in studies with more detailed smoking information.

The relationships between smoking during pregnancy and poor birth outcome, including SIDS, are well known.[2,16,17] Additionally, associations between the involuntary exposure of infants to cigarette smoke after birth and health problems are a public health concern.[11,12] This analysis indicates that an infant's exposure to tobacco smoke after birth is independently associated with death from SIDS. Obstetric and pediatric practitioners should take that information into account when discussing health practices and habits with families.

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OTITIS MEDIA ("GLUE EAR")

In addition to claims that parental smoking affects the respiratory health of children, there are claims that exposure to parental smoking might increase the risk of otitis media (commonly known as "glue ear") in children. Otitis media is an inflammation of the inner ear that often leads to an accumulation of fluid in the inner ear canal. Otitis media often appears as a complication of various viral and bacterial infections, including measles. If left undetected, otitis media can lead to hearing loss and learning disabilities. Authors of studies examining this issue have not formulated a widely accepted mechanism for how ETS might increase the risk of otitis media in children. There are two theories that are proposed but have not been scientifically proven: 1) One theory is that ETS somehow chronically irritates the eustachian tube of the inner ear, leading to the inflammation; and 2) The second theory is that ETS potentially increases the risk of upper respiratory tract infections that spread to the inner ear. The results of the studies on this subject are variable and are subject to the same confounders that potentially bias the results of studies on other ETS related issues. While the science on this issue is controversial, the reported seriousness of otitis media makes investigators anxious to make recommendations for child safety. However, the studies on otitis media and parental smoking have not established a clear association.

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Lung Function/Disease: Adults

The issue of a possible relationship between exposure to ETS and respiratory disease in nonsmokers was first raised in a 1980 study by two California researchers, White and Froeb.[1] On the basis of their measurements of the small airways function of smokers and nonsmokers in the workplace, they asserted that nonsmokers exposed to tobacco smoke at work for 20 or more years had reduced function of the small airways compared to nonsmokers who did not have such exposures. Other studies with similar findings have been reported since that time. In 1983, French researchers Kauffmann, et al., reported that nonsmoking spouses over 40 years of age who were married to smokers exhibited decreases in pulmonary function compared to nonsmoking spouses of nonsmokers.[2] A 1989 study by Hole, et al., of a Scottish population reported significantly lower pulmonary function among nonsmokers who lived with smokers compared to nonsmokers who were not exposed to ETS.[3]

However, each of these studies, particularly the White/Froeb study,[4-7] has been criticized for numerous reasons. In regard to the White/Froeb study, for example, a physician at a U.S. medical school questioned their use of carbon monoxide as an index of smoke exposure, contending that they "do not have reliable estimates of the smoke exposure in the environment of their nonsmokers" because it is not unique to tobacco smoke.[7] A British

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reviewer shared the physician's view that their findings "relate to an index which is contentious and certainly not an accepted reliable indicator of an increased health risk."[8] White and Froeb themselves noted that the average values of the pulmonary tests of nonsmokers exposed to tobacco smoke "were not notably different" from the values suggested as normal by a specialist in this area.[9]

Perhaps the most telling criticisms of the study were voiced by Dr. Michael Lebowitz of the University of Arizona at an annual joint meeting of the American Lung Association/American Thoracic Society and in a subsequent letter published in the U.S. Congressional Record.[10-11] During a forum at the ALA meeting, Dr. Lebowitz stated that he had concluded, from his own extensive review of the study and from an interview with White, that the study was "improperly designed" from an epidemiological point of view. He noted that there were problems "inherent" in the study, including the selection of the study group and the measurement of smoke in the workplace. Dr. Lebowitz also expressed concern that the statistical significance of the data appeared to depend on the unexplained omission of data for 3,000 people who were originally included in the study. Based upon these considerations, Dr. Lebowitz urged that the study not be used to support the claim that ETS affects the lung function of adults in the workplace.

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Dr. Lebowitz again took issue with the White/Froeb study in 1984 in a paper he presented at the Vienna Symposium on Passive Smoking. He contended:

> Even with a biased population, poor study design, and incorrect statistical evaluation, there were no clear-cut, consistent, medically meaningful differences between passive smokers and groups of nonsmokers; a corrected statistical analysis strengthened this conclusion.[12]

In the same paper, Dr. Lebowitz also questioned the findings of the 1983 French study which reportedly found significant differences in lung function between exposed and nonexposed nonsmokers in one part of the study population but no significant differences in the population as a whole. Dr. Lebowitz noted that since the "healthiest" part of the study population lived in the most polluted areas, the study may have been flawed due to biased population selection and testing or other confounding factors.[12]

In addition to these concerns, the results of the White/Froeb, the French and the Scottish studies appear to be inconsistent with other research on lung disease and lung function in nonsmokers. For example, a 1984 study of 1,351 German office workers by Kentner, et al., reportedly found no effect of ETS on pulmonary function among exposed nonsmokers.[13] In a 1988 update

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of the study, the investigators noted that "there is no evidence that average everyday passive smoke exposure in the office or at home leads to an essential reduction of lung function in healthy adults."[14] The key investigator for the study reported these same findings in 1989 and 1990 publications.[15,16]

Similarly, Canadian researchers Shephard, et al., reported that their analysis of a group of healthy young adult nonsmokers showed "no consistent reaction" of static lung volumes and insignificant changes of other lung function measurements when they were exposed to tobacco smoke.[17]

Numerous studies of individuals exposed to ETS in the home also present conclusions which appear to be contrary to these three studies. In 1981, Comstock, et al., epidemiologists at the Johns Hopkins University School of Medicine in New York, reported that in a group of 1,724 adults, the frequency of respiratory symptoms in nonsmokers was not significantly associated with the number of smokers in the household.[18] Nor was the frequency of impaired ventilatory function significantly higher if there were smokers in the home. However, their analysis did show that "among men who never smoked cigarettes, gas cooking was definitely associated with impaired ventilatory function, even when corrected for multiple comparisons."

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Other studies on pulmonary function, respiratory disease and environmental tobacco smoke deserve special mention. In 1983, for example, Jones, et al., reported that in a case-control study of several hundred nonsmoking women from a U.S. study population, there was no significant association between decreases in lung function and exposure to ETS in the home.[19] Similarly, Lebowitz, et al., coordinators of an epidemiologic study of obstructive lung disease in Arizona, reported finding no effects from ETS exposures in the home in their adult study population.[20] In a study of 376 families, Yale University scientists Schilling, et al., also reportedly found no evidence that environmental tobacco smoke affects either lung function or respiratory symptoms in adults.[21]

More recently, in a Canadian study on the effect of indoor and outdoor pollutants on the lung function of housewives, Hosein and Corey concluded that ETS exposure did not significantly influence lung function, but that gas stove usage played a role in average lung function decline.[22] These findings have been reported by others. For example, a Japanese research group, Nitta, et al., has also reported that gas stove usage affects the respiratory health of adults.[23] Koo and Ho recently studied the effects of indoor nitrogen dioxide (NO_2) levels on respiratory illness rates in Hong Kong.[24] They reported that indoor NO_2 levels were associated with allergic rhinitis and chronic bronchitis in non-

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smoking mothers, but that there was no relationship between environmental tobacco smoke and NO_2 levels in the home environment.

In 1990, a Greek research group, Kalandidi, et al., investigated the possible relationship between reported tobacco smoke exposure and chronic obstructive pulmonary disease (COPD) in adult nonsmokers.[25] Although they reported finding increased risks of COPD among nonsmokers reportedly exposed to ETS, it is not clear whether they adequately considered other potential exposures which have been associated with the development of COPD such as occupation and outdoor air pollution. Another study published in 1990 by Lebowitz and Quackenboss reported that while they observed an increase in several acute respiratory symptoms associated with exposure to ETS, they noted "no relationship between the prevalence rates for chronic symptoms and diseases and the presence or amount of ETS in the home."[26]

In 1990, Jedrychowski, et al., reported an increased occurrence of respiratory illness among a group of elderly women exposed to ETS, but conceded that the reported effects were "greatly confounded by other indoor pollutants, especially those associated with cooking the meals on gas ovens." They also conceded that they considered only "the current passive smoking experience at home and took no account of the history of passive smoking that

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might have been present in the work place," which could "evidently bias the results of the study with respect to passive smoking."[27]

Researchers who have analyzed these reported findings contend that the results are mixed and inconclusive. For example, researchers in France, Laurent, et al., have commented that purported long-term health effects from exposure to ETS are difficult to demonstrate in healthy adults and that the results of the epidemiological studies are "sometimes conflicting and often open to question."[28] One investigator who is critical of ETS conceded that "the effect of passive smoking on respiratory infections in adults has not been well characterized and reports of its effects on chronic respiratory disease in adults have been inconsistent."[29]

In his summary of the studies of respiratory symptoms and disease in adults published up to early 1990, American investigator Dr. Philip Witorsch noted that "4 of 8 [reported] an increased frequency, 4 of 8 no increased frequency."[30] He stated that, in addition to "all of the problems" with the studies, "these results are too variable to permit any conclusion of association." As his summary demonstrates, the conclusion of the participants at the 1983 U.S. National Institutes of Health workshop on ETS exposure, that the possible effect from ETS "varies from negligible to quite small,"[31] is still pertinent.

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"Compromised Individuals": Adults

Asthmatics are believed to be particularly vulnerable to various environmental influences, including ETS, but the scientific data in this area are contradictory and inconclusive. A 1981 study by Dahms, et al., for example, reported decreases in the pulmonary function of several asthmatics exposed to environmental tobacco smoke.[1] However, the study suffers from several obvious limitations, including the unrealistic conditions under which the subjects were exposed to ETS; they were challenged with high levels of smoke in an enclosed smog chamber. In addition, as the authors themselves noted, their experiment lacked proper controls and the effects observed may have been due to psychological, not physical, factors.

Contrary to Dahms, et al., a Canadian group, Pimm, et al., observed no systematic lung changes among asthmatics exposed to levels of tobacco smoke typically found in public places.[2] Later research by the co-authors of this study supports this conclusion. They reported that respiratory data collected from a group of asthmatic volunteers exposed to tobacco smoke "do not suggest that asthmatic subjects have an unusual sensitivity" to such exposure.[3] Although several volunteers claimed to have experienced wheezing and tightness in the chest due to the exposure, the researchers determined that the "physiological data give little

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support to the concept of a subgroup with particular sensitivity." They noted that these reactions probably were due to the "suggestibility" of the subjects.

The difficulty in determining the impact of psychological responses in such studies is clearly demonstrated by the results of two reports from Australia. Although a 1985 report by Knight and Breslin suggests that short-term ETS exposures are capable of inducing reactions in asthmatics,[4] an earlier study co-authored by Breslin tends to support the theory that psychological reactions may partially explain symptoms observed during such exposures. In that study, Breslin and Ing reported that although asthmatics exposed to tobacco smoke complained of subjective symptoms, no significant objective evidence of airways obstruction was observed.[5]

Other studies also fail to provide support for claims regarding a relationship between ETS exposure and reactions in asthmatics. For example, Wiedemann, et al., at Yale University, examined the short-term effects of ETS exposure on a group of young asthmatic patients and observed no changes in lung flow rates.[6] They concluded that such exposures present "no acute respiratory risk" to asthmatics.

Tulane University scientists Stankus, et al., recently assessed the effects of heavy exposure to ETS in a group of self-

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reported "tobacco smoke-sensitive" asthmatics. They reported that two-thirds of the subjects did not experience significant changes in pulmonary function even after heavy, prolonged exposure to ETS, and that there was no association between reactions to ETS and hypersensitivity to tobacco leaf extract, which is commonly used in allergy testing.[7]

A report by Lebowitz on data from a large-scale epidemiological study in the U.S. suggests that ETS in the home does not affect symptoms or pulmonary function in either children or adult asthmatics, but that dust and pollen in the home apparently can provoke such effects.[8] Another group of U.S. researchers, Bailey, et al., also recently reported that exposure to ETS did not impair lung function in 263 asthmatic adult subjects.[9]

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Lung Function/Disease: Children

Perhaps no claim regarding ETS is as capable of provoking strong feelings as the charge that parents who smoke may harm the health of their children. While the issue of parental smoking is laden with emotion, the scientific basis for the claim is difficult to interpret. For example, while one study examines respiratory symptoms or illness such as coughs and colds by questionnaire responses from parents,[1] another measures lung function with special equipment at a school or health facility.[2] In the U.S. alone, according to one report, this has led to a situation in which studies of ETS and the respiratory system are "being carried out by at least three different groups, are employing different populations and methodologies and have led to varying conclusions."[3]

Perhaps not surprisingly, such studies, each with a different sample size, data collection method, and analysis, tend to yield factually incompatible and contrary conclusions. For instance, although certain studies have reported adverse findings between parental smoking and respiratory illness in children,[4-35] others have observed no significant relationship.[1,36-51] After a five-year study of over 400 children, for example, a Dutch research group concluded there was "no evidence" that parental smoking had an appreciable effect on respiratory symptoms in school children.[43]

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A similar conclusion was reached by a group of U.S. researchers, including a critic of smoking, who found "no significant relation" between parental smoking and respiratory symptoms in a study of nearly 400 families with 816 children in three cities.[36]

The contradictory nature of findings on the issue of parental smoking is also apparent in the growing number of studies examining the relationship between parental smoking and children's respiratory or lung function. Although several reports have claimed that parental smoking results in decreased pulmonary function in children,[8,13-14,32,52-60] others have not,[61-64] including those of a U.S. research group who have published a series of studies on this subject.[2,65-67] In 1982, for example, the U.S. group showed that a comparison of body size with lung function eliminated any reported correlation between parental smoking and children's lung function.[2] Two years later, a reanalysis of data from families in their study population again showed that "parental smoking did not have a significant effect on children's pulmonary function; smoking habits of others in the household (predominantly siblings) did not have any effect either."[66]

Moreover, the authors of studies reporting adverse effects from ETS exposures among children concede that their conclusions must be viewed with caution because of numerous confounding factors. The potential impact of such factors was given special consideration

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in the report from a workshop on ETS sponsored by the U.S. National Institutes of Health.[3] After listing numerous such factors, including types of heating used, socio-economic status and demographic and medical characteristics of the study population, the report cautioned "that any study which ignores them will be seriously flawed."

The importance of such factors in evaluating the outcome of research on parental smoking is supported by a number of reports which have shown that the use of gas stoves in the home may be independently associated with respiratory disease[40,65,68-72] and impaired pulmonary performance[73-74] in children. One group of British researchers acknowledged the possible influence of factors such as cross-infection in the home and genetic susceptibility to childhood respiratory illness and symptoms.[11-12] More recently, researchers in Hong Kong reported "a highly significant correlation" between the frequency of respiratory illnesses of mothers and their children.[75]

Other confounding factors independent of parental smoking have been reported recently in the literature. For example, studies in the United Kingdom have identified damp housing[46, 76-79] and paternal occupation[80] as potential explanatory factors for the occurrence of respiratory illness in children. Other recent studies have identified outdoor air pollution,[82-85] infections

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transmitted during day-care attendance[49,86-87], decreased breast-feeding[88] and the use of kerosene heaters and woodburning stoves in the home[89-91] as factors related to childhood respiratory disease.

The relevance of dampness in the etiology of respiratory symptoms in children is supported by current research which links dampness with the presence of molds, dust mites, fungi and other allergenic microbes. The growth of fungi and molds in the home is directly related to respiratory symptoms and sensitization reactions in some individuals.[78,92-94] Recent investigations report, moreover, that exposure to ETS does not increase sensitization to common allergens in children.[95-96]

Others have conceded that the reliance of such studies on questionnaires for information about respiratory symptoms casts doubt on their reported findings. In one study that reported a significant association between parental smoking and respiratory symptoms, for example, it was noted that even "slight changes" in the way the questions were phrased could result "in substantial differences in the type of responses one obtains."[14] Similarly, another study observed that there was a significant difference in the respiratory symptoms reported depending on which parent completed the questionnaire.[24] Authors of another study that reported adverse effects of parental smoking on the respiratory

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health of children conceded that "since the exposure variables used in these analyses were subject to substantial measurement error, a more refined measurement of personal exposure is required."[29] One researcher who is critical of parental smoking has stated that "quantitative assessment of involuntary exposure of infants and children to ETS has been very imprecise and probably inaccurate."[97]

Studies utilizing seemingly more objective standards such as actual measurements of lung function are also open to criticism. Even reviewers of the literature who are critical of parental smoking concede that the tests used in these studies are "influenced by a large number of variables."[98] They list age, height, and gender of the test subject as well as his or her motivation, cooperation, and effort put forth during the test, the skill and experience of the operator, and the type of instrumentation used as variables that can affect the results of pulmonary function measurements. The reviewers explain that these problems are especially important in pulmonary function measures taken in children. In 1989, two American co-researchers, Witorsch and Witorsch, reported that "it has been shown that mean pulmonary performance within a single group of children can vary significantly from one spirometry test to the next without any apparent cause" and that it "is noteworthy that such statistically significant

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differences are similar in magnitude to most of the small decrements in pulmonary function reported in children of smoking parents."[99]

The shortcomings of studies analyzing the relationship between ETS exposure and childhood health were highlighted in a 1988 report by two U.S. investigators who re-examined 30 such studies and evaluated them for their scientific validity.[100] They noted that while several studies of adequate scientific design had reported a statistically significant relationship between ETS exposures and childhood health, "most studies had significant design problems that prevent reliance on their conclusions." The authors concluded that "many questions remain, and future studies should consider important methodological standards to determine more accurately the effect of passive smoking on child health."

Thus, claims that parental smoking plays a causal role in the development of respiratory symptoms and reduced lung function in children are not scientifically justified. Such claims are typically based upon a single study of a selected symptom (such as cough or wheeze). These kinds of studies invariably fail to consider nutrition, health habits of the family, and other lifestyle variables. Similarly, studies that report reduced lung function in children of smoking parents fail to address the issue of socio-economic status or the potential role of genetic and family traits in pulmonary function capabilities.[64] Moreover, the reductions

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reported in the literature are small and of uncertain clinical or biological significance, and are contradicted by a number of studies that reportedly have observed no effect of parental smoking on children's lung function.

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"Compromised Individuals": Children

As with studies of adults who have chronic lung problems, the data on parental smoking and its possible effects on children with lung conditions are inconclusive.[1-9] In 1990, German researchers Oldigs, et al., reported that exposing children with bronchial asthma to cigarette smoke sufficient to reach a level of 20 parts per million (ppm) carbon monoxide for one hour did not affect their lung function or bronchial responsiveness.[8] Similarly, Charles Sherman and his co-investigators reported that neither paternal nor maternal smoking "bore an apparent relation to the development of asthma" in a sample of children, aged 5 to 9, enrolled in public and parochial schools in East Boston, Massachusetts in 1974.[9]

A British researcher, Strachan, has implicated damp housing as a potential factor in the development of childhood asthma.[10] After controlling for the possible influence of housing tenure, number of people per room, number of smokers in the household, and gas cooking, he reported that the relationship between damp housing and childhood asthma in his study population remained "highly significant."

Other investigators, Rubin and Gilljam, et al., have suggested that parental smoking might worsen the condition of

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children with cystic fibrosis, a congenital disease usually developing during childhood and causing pulmonary disorders.[11-12] However, these studies are subject to the same uncertainties exemplified by other studies on parental smoking. For example, although Rubin reported an association between parental smoking and decreased nutritional status and growth of children with cystic fibrosis, he conceded that "the possibility cannot be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the child."[11]

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